# APPENDIX 5

## EXAMPLES OF RISK ASSESSMENTS THAT GROSSLY OVERSTATE RISK

Table of Contents

## I. Human Health Risk Assessment Examples

### A. Exposure Assessment

The first, and probably least controversial, task in human health environmental risk assessment (HHRA) is environmental sampling and analysis.[1] The second task is exposure assessment. This critical task involves measuring or estimating all parameters necessary to estimate, or model, mean and high-end human exposure to the chemical of interest through the scenario being assessed (e.g., exposure to a chemical that was disposed of in a landfill or exposure to combustion sources of air emissions). There are typically numerous steps in exposure assessment, including site/setting characterization, identification of fate and transport mechanisms, identification of potentially exposed populations, determination of direct and indirect (and complete and incomplete) exposure pathways, measurement/estimation of exposure parameter values or probability distributions (e.g., exposure frequency, exposure duration, or ingestion rate), and measurement or estimation of exposure point concentrations. Whenever possible, these steps should be based on site-specific data. Reliance on default assumptions should be avoided and used only when site-specific data are unavailable. In its Guidelines for Exposure Assessment, EPA (1992a) states:

> General default values should not be used in place of known, valid data that are more relevant to the assessment being done. The use of generic or surrogate data is common when site-specific data are not available. [However,] this is an additional source of uncertainty, and should be avoided if actual data can be obtained.

The final step in exposure assessment is calculating time-weighted intakes which are later combined with the toxicity assessment to characterize the risk. Time-weighted averages can be calculated using either a point estimate approach or a probabilistic method (such as Microexposure Event Modeling). For noncarcinogens, the time-weighted average is expressed as the average daily dose (ADD); for carcinogens, it is expressed as the lifetime average daily dose (LADD).

Although EPA is generally conservative in all aspects of exposure assessment, the Council has found that most of EPA's overconservativeness has been in estimating exposure parameters, including the magnitude, frequency and duration of exposure. The following examples illustrate the degree to which the Agency uses exposure factors that substantially overstate human exposure to chemicals in the environment.

[1] Steps in this task include collecting and compiling all existing, relevant data, determining whether additional data are required, collecting and analyzing new data, and data validation.

EPA Exposure Assessment Requirements in Connection with Petition for "Delisting" of Gas Turbines from MACT Requirements

Recently, the Gas Turbine Association petitioned EPA to "delist" gas turbines from MACT requirements pursuant to Section 112(c)(9) of the Clean Air Act on the grounds that gas turbine emissions present less than a $10^{-6}$ risk of cancer and an insignificant non-cancer risk. Section 112(c)(9) authorizes EPA to exempt source categories from MACT upon a showing that that no source in the category emits "hazardous air pollutants in quantities which may cause a lifetime risk of cancer greater than one in one million to the individual in the population who is most exposed to emissions of such pollutants" and, in the case of non-carcinogens, that emissions do not "exceed a level which is adequate to protect public health with an ample margin of safety and no adverse environmental impact will result." The petition is based on the fact that hazardous air pollutant (HAP) emissions from turbines are miniscule -- HAPs are emitted in the part per billion or part per trillion range, and the largest modeled impacts are less than 10% of ambient levels of HAPs.

GTA has been working to satisfy EPA's delisting requirements. Although EPA has stated that it is supportive of GTA's effort, the Agency is insisting that the risk assessment be conducted using exceedingly conservative exposure factors[2]:

- GTA's initial risk assessment used a 30-year exposure scenario. A 30-year exposure period is conventionally used in hazardous waste incinerator risk assessments to evaluate reasonable maximum exposure and is consistent with EPA's Risk Assessment Guidance for Superfund and Exposure Factors Handbook (EPA, 1989; EPA, 1997b). Based on national statistics, 30 years represents the upper-bound ($95^{th}$ percentile) number of years that an individual might live at the same residence, while nine years represents the average number of years ($50^{th}$ percentile). See Table 15-176 of EPA (1997b). EPA, however, has insisted that GTA use a lifetime exposure period of 70 years, with the first six years of exposure assumed to be childhood exposure.
- Although it is true that the statute requires that the delisting risk assessment be conducted using the most exposed individual, EPA is interpreting this requirement unreasonably. EPA insists that the risk assessment assume that the maximally exposed individual never leaves the point of maximum exposure (e.g., never goes to school or work) over a period of 70 years.
- EPA has demanded that GTA use the highest emission factor in EPA's database for turbine emissions, rather than the average.

[2] As discussed below, USEPA is also demanding that GTA use a very conservative approach to toxicity assessment.

## Fox River Human Health Risk Assessment

The RI/FS for the Fox River/Green Bay Superfund Site was prepared by a contractor under oversight by the Wisconsin Department of Natural Resources (WDNR) and USEPA. The RI/FS includes a human health risk assessment (HHRA) of risks posed by PCBs in sediments at the site. The PCBs are taken up by fish and pass through the food chain to animals that feed on fish. Based on both the human health risk assessment and an assessment of ecological risks, USEPA and WDNR have issued a Record of Decision (ROD) calling for dredging of approximately five miles of the River. A ROD choosing a remedy for other portions of the River is expected this summer.

The HHRA substantially exaggerated human health risk in at least three respects. First, the HHRA relied on inappropriate estimates of the fish consumption rates of anglers who fish the Fox River. Second, the HHRA used unrealistic fish tissue concentrations because it: (a) relied on 1990's fish tissue data that do not reflect existing and future, declining, fish tissue concentrations; and (b) assumed, incorrectly, that the exposed population consumes a significant amount of carp. Third, the HHRA did not correctly adjust for the mobility of the population and thus overstated exposure duration. Based on these three factors, the HHRA likely exaggerates human health risk by several orders of magnitude. These factors are discussed briefly in turn.

*Fish Consumption Rate*

In order to assess risks to recreational anglers who consume fish from the Fox River fish, it is necessary to use fish consumption data that reflect the long-term consumption habits of recreational anglers who actually use the fishery. However, the studies relied on by the HHRA (West et al. 1989a; 1993) do not provide data for people who fish the Fox River and do not provide reliable estimates of long-term consumption rates because the studies collected only short-term data. The study design used in the West et al. studies collected data on the consumption habits of Michigan anglers using a one-week recall period. As EPA acknowledges in its Exposure Factors Handbook (EPA, 1997b), "the distribution of average daily intake reflective of long-term consumption patterns cannot in general be estimated using short-term (e.g., one week) data." EPA (1997b) itself has concluded that the West et al. (1993) study should not be used to estimate long-term consumption rates, stating that "the resulting distribution [of the West et al. (1993) study] will not be indicative of the long-term fish consumption distribution and the upper percentiles reported from the EPA analysis will likely considerably overestimate the corresponding long term percentiles" (EPA, 1997b).

Using upper percentile consumption rates from the West et al. (1993) data resulted in significantly inflated consumption rates. The HHRA should instead have used readily-available data from the Wisconsin Fishing and Outdoor Recreation Survey (WFORS) which provides long-term consumption data obtained from Wisconsin, rather than Michigan, anglers. In this study, data were recorded by anglers in diaries that were maintained over a period of four months. This data collection methodology both minimized potential recall bias and provided data on long-term behavior. As a result, far fewer simplifying assumptions are needed to extrapolate

these data to annualized fish consumption rates. Using the WFORS data rather than the West at al. data would lower the Fox River risk estimates by at least a factor of two.

*PCB Concentration in Fish*

The HHRA used inappropriately high estimates of PCB fish concentrations because: (a) it relied on 1990's fish tissue data that do not reflect existing or future, declining concentrations of PCBs in Fox River fish; and (b) it assumed, incorrectly, that the angler population consumes a significant amount of carp, a fish that accumulates higher concentrations of PCBs than other species. These errors increased the HHRA's estimates of risk by the following factors.

- Failure to use current and future PCB concentrations in fish – factor of 10. The HHRA averaged PCB fish concentrations for the 1990s, and assumed that these concentration remained static into the future. Large-scale fish sampling conducted in 1998 by the Fox River Group (FRG) demonstrated significant declines in fish tissue PCB concentrations. Using principally these 1998 data for purposes of calculating risk resulted in a 10-fold reduction in PCB fish tissue concentrations, on average. Moreover, results of food web modeling suggest that PCB tissue concentrations will continue to decline over time.
- Assuming high consumption of carp – factor of 1.3 to 30. The HHRA assumed that recreational anglers consume a large amount of carp. The FRG's review of angler surveys for the Lower Fox River indicated that carp were rarely caught and eaten. Because carp contain a higher relative percentage of lipids, they generally also have higher PCB tissue concentrations.

The total impact of these two factors is multiplicative, so the total increase in risk estimates based on errors in defining PCB concentration in fish is between 13 and 300.

*Population Mobility*

The HHRA assumed exposure durations that were far too long because it ignored population mobility. For the hypothetically highly-exposed individual (referred to as the "Reasonable Maximum Exposed" individual or "RME" individual) and the typically exposed individual (referred to as the "Central Tendency Exposure" individual or "CTE" individual) the HHRA assumed exposure durations of 50 and 30 years, respectively. There is no valid basis for these exposure durations. USEPA's Exposure Factors Handbook (EPA, 1997b) recommends point estimate exposure duration values for the RME and CTE individuals of 30 and 9 years, respectively, and notes that at least three studies support these values. The HHRA's departure from the accepted exposure values results in increases of the RME risk by a factor of more than 1.5 and increases of the CTE risk by a factor of more than 3.

The combination of these errors results in exaggeration of the risk posed by consumption of Fox River fish by as much as two orders of magnitude.

Upper Hudson River Human Health Risk Assessment[3]

EPA's HHRA for the Upper Hudson River substantially overestimates human health risk for several reasons. Primary among these is that the HHRA grossly overstates the rate at which Upper Hudson River anglers might consume fish from the River.

Because EPA failed to conduct a fish consumption survey of anglers who might use the Hudson River, it was forced to rely on studies of other water bodies and angler populations. However, although there are five studies that might have been used to estimate Upper Hudson River angler fish consumption, EPA chose to rely on a single study, Connelly et al. (1992). This study reported rates of fish consumption that are about four times higher than the average of the other studies (EPA, 2000f).

EPA's use of the 1992 Connelly study to estimate fish consumption rates was inappropriate for several reasons. First, EPA derived a consumption rate for fishermen almost three times greater than the authors of the study found. The paper states that the average number of meals consumed by responding anglers was 11 meals per year which, using a 0.5 pound meal size, results in a mean consumption rate of 6.8 g/day instead of the 17.3 g/day calculated by EPA (Connelly, et al., 1992). Next, the study was not designed to assess consumption rates, but rather angler awareness of and knowledge about fish consumption advisories. As a result, numerous assumptions were required to generate consumption rates (e.g., meal size, types of Hudson River fish eaten, the type of waterbody the surveyed anglers fished in, etc.). Third, individuals who do not respond to surveys of this type are likely to consume considerably less fish than individuals who do respond (Connelly et al., 1992; West et al., 1989a,b). The 52.3% response rate reported by Connelly is on the low-end of acceptable standards, which biases fish consumption estimates toward higher level consumers, leading to an overestimate of fish consumption rates. EPA itself recognized that some of the rates generated in the 1992 Connelly study were beyond credibility. The Agency discarded some of the high end consumption results and used the 90th percentile, rather than the usual 95th percentile, in its point estimate for the high end of exposure (EPA, 2000f). These and other limitations led EPA itself to conclude that the study should not be considered a "key" study when evaluating freshwater fish consumption by recreational anglers (EPA, 1997b).

Most importantly, consumption rates based on Connelly et al. (1992) are inconsistent with well-conducted studies of similar angler populations which are more appropriate for estimating rates of fish consumption for the Upper Hudson. See Table 1.

[3] As set forth in EPA's "Phase 2 Report – Review Copy, Further Characterization and Analysis, Volume 2f – Human Health Risk Assessment, Hudson River PCB Reassessment RI/FS."

**Table 1: Comparison of Fish Ingestion Rates (g/day) from Studies of Northeastern Recreational Anglers**

| Consumption Rate Percentile | Connelly et al. (1992) New York Multiple Rivers[a] | Ebert et al. (1993) Maine Multiple Rivers | ChemRisk (1991) Maine Single River[b] | Connelly et al. (1996) New York All Waters[c] | Ebert et al. (1996) Connecticut Single River[d] |
|---|---|---|---|---|---|
| 50th | 4.0 | 0.99 | 0.49 | 2.2 | 0.17 |
| 90th | 31.9 | 6.1 | 5.3 | 13.2 | 5.8 |
| 95th | 63.4 | 12.4 | 10.7 | 17.9 | 12 |
| Arith. Mean | 17.3 | 3.7 | 3.0 | 4.9 | 2.6 |

a. EPA (2000f) analysis
b. West Branch Penobscot River
c. EPA (2000f) analysis
d. Housatonic River

Each of the studies listed in the table (other than Connelly et al., 1992) was designed specifically to assess rates of fish consumption. Further, for example, in their 1996 study, Connelly and co-workers substantially reduced the possibility of recall bias by using food diaries, which tend to better represent long-term consumption habits (Connelly et al., 1996). Moreover, Connelly et al. (1996) and Ebert et al. (1996) also had higher rates of response and were, therefore, more representative of the targeted angler population. Finally, with any of the four alternative studies, there is no need to assume an arbitrary meal size in order to derive consumption estimates. Based on these facts, it is clear that using Connelly et al. (1992) skewed EPA's estimates of exposure. The evidence of the relevant angler surveys taken as a whole is that realistic estimates of fish consumption are approximately one-quarter of those assumed by EPA: i.e., 1 meal per month for the high exposure angler.

Housatonic River -- Upper Two Miles Human Health Risk Assessment

In May 1998, EPA and the Commonwealth of Massachusetts Department of Environmental Protection (MDEP) published a memorandum titled "Evaluation of Human Health Risks from Exposure to Elevated Levels of PCBs in Housatonic River Sediment, Bank Soils and Floodplain Soils in Reaches 3-1 to 44-6 (Newell Street to the Confluence of the East and West Branches)" (Housatonic Two-Mile HHRA). This HHRA covered a two-mile stretch of the Housatonic River within the City of Pittsfield, Massachusetts, and was used by EPA as the basis for requiring cleanup of that stretch of the river. The HHRA envisioned three hypothetical receptor scenarios involving exposure to PCBs along different areas of the river reach in question:

- EPA assumed that in Exposure Area A, where the river is bordered primarily by commercial properties, 9 to 18-year-old children would trespass along the river banks ("youth trespasser scenario").
- EPA assumed that in Exposure Area B, where the river is bordered by residential properties and the banks are moderately steep, children between the ages of 5 and 12 years of age would wade in the water and play in and along the river banks ("child wader scenario").
- EPA assumed that in Exposure Area C, where the river is bordered by residential properties and the banks are not steep, children between the ages of 1 and 6 years old would wade in the water and play in and along the river banks ("child resident scenario").

EPA then estimated cancer and non-cancer risks to these hypothetical populations using a variety of exposure assumptions. Among these assumptions were that:

- The youth trespasser would contact soils and sediments along the river two days per week every week from April through October (61 days per year) for nine years. Each time he visited the river, he would get soil or sediment all over his hands, arms, feet and lower legs (843 square inches – or almost 6 square feet -- of skin). The soil/sediment would remain on the skin for 24 hours.[4] The youth would also eat 50 milligrams of soil each and every day he visited the river. Finally, the soil that was contacted or ingested would always be contaminated with virtually the highest concentration of PCBs that had been detected in soils and sediments of the river reach (rather than the average).[5]

[4] This assumption is inherent in the agencies' use of the assumption that 14% of the PCBs contained in the soil which the children contact would be absorbed through the skin. This factor was taken from Wester et al. (1993), in which monkeys were found to absorb this fraction of PCBs over a period of 24 hours when PCB-containing sand was stuck to a shaved area of their bodies with a patch. (Note that this sand had a very low organic carbon content, which would tend to make PCBs more bioavailable than they would be in soil with higher organic carbon; a more recent study of monkeys using soil that contained an organic carbon content more typical of U.S. soils found that the absorption rate was only approximately 4%. Mayes et al. (2002).)

[5] For exposure point concentration, the agencies used the 95 percent upper confidence limit ("$UCL_{95}$") on the mean, unless this value exceeded the maximum concentration, in which case the maximum was used. These values were much higher than the actual mean. For example, for Exposure Area A, the mean sediment and soil concentrations were 17 and 275 ppm, respectively. The values used by the agencies were 46 and 2,400 ppm, respectively.

- The child wader was assumed to contact soils along the river five days per week every week from April through October (153 days per year) and to contact sediments in the river five days per week every week from June through August (65 days per year). This remarkably consistent behavior would go on for seven years. Like the youth trespasser, the child wader would get soil or sediment all over a large portion of her body (570 $in^2$ of skin for soil and 832 $in^2$ of skin for sediment) each time she visited the river, the soil/sediment would adhere for 24 hours, she would eat 50 milligrams of soil/sediment per day of exposure, and the soil/sediment contacted or ingested would be the most contaminated soil or sediment available.[6]
- The same exposure frequency assumptions that were used for the child wader were used for the child resident, and the behavior was assumed to last five years. The child resident was assumed to get even dirtier than the child wader in proportion to her size, having 445 $in^2$ of skin exposed to soil and 661 $in^2$ of skin exposed to sediment for 24 hours. The child resident would eat 100 milligrams of the most contaminated soil or sediment available on each such day.[7]

These exposure assumptions are clearly excessive in terms of PCB concentration, exposure frequency[8], exposure duration, and extent of skin exposure. But just as important, as explained in a report titled "Critique of Agencies' Human Health Risk Assessment for the Two-Mile Reach (July 7, 1998)" (Critique) that was prepared by ChemRisk and submitted to EPA and MDEP by General Electric, actual blood PCB concentration data taken from residents of Pittsfield, including those who lived along the river, showed that these residents who did not have occupational exposure to PCBs did not have elevated levels of PCBs in their bodies. Rather, their blood PCB concentrations were within the background range (mean of 4 to 8 ppb) for non-occupationally exposed populations in the U.S.[9] Thus, the agencies' human health risk assessment for this reach of the Housatonic River was not only overconservative, but also inconsistent with the actual empirical data.

[6] For example, for Exposure Area B, the mean sediment and soil concentrations were 89 and 36 ppm, respectively. The values used by the agencies were 905 and 377 ppm, respectively. Using the 905 ppm value is particularly egregious. Four samples taken in very close proximity to the location where the 905 ppm concentration was found had PCB concentrations ranging from 1.6 to 51 ppm, or 18 to 566 times lower.

[7] For example, for Exposure Area C, the mean sediment and soil concentrations were 16 and 23 ppm, respectively. The values used by the agencies were 30 and 68 ppm, respectively.

[8] For example, Exposure Area A is primarily commercial, with riverbanks that are steep, heavily vegetated, fenced and posted with signs that warn of the presence of PCBs. The HHRA assumed that individuals would frequent this area two days per week for seven months of the year. Although individuals might conceivably trespass here occasionally, it was unreasonable to assume that individuals would trespass on such a regular basis.

[9] These findings are consistent with studies that have been performed near other PCB-contaminated sites in Norwood, Canton, and Fairhaven Massachusetts, Paoli, Pennsylvania, Milford, New Hampshire, and Bloomington, Indiana.

Manistique Harbor Contaminated Sediment Site

The Baseline Human Health Risk Assessment (BHHRA) for the Manistique Harbor Sitecalculated a cancer risk to the average and "high-end" recreational angler of 1.8 x 10-5 and 2.4 x 10-3, respectively. {Note: Using the current CSF for PCBs of (2.0 mg/kg/d)-1, these cancer risks would be 4.6 x 10-6 and 6.2 x 10-4, respectively]. For the "average" and "high-end" subsistence anglers the risks were 2 x 10-4 and 1.2 x 10-2, respectively. These cancer risks estimates were used by Region 5 risk managers to require remediation of the Manistique Harbor sediments.

The BHHRA incorporated numerous overly conservative assumptions and the result was a remedy that has to date cost in excess of $48 million. If a more reasonable, appropriate, and scientific assessment of the Harbor was conducted, it would have been determined that the levels of PCBs in surface sediments posed significantly less or no risk to human health or the environment. This would likely have led to a less rigorous remedy, or possibly a determination that remediation was not needed.

The folloing are examples of some of the redundant conservatism inherent in the BHHRA:

- The high-end angler scenarios (both recreational and subsistence) assumed that 25% of the diet (consumption of 54 and 130 g/day every day for 30 years) was carp, despite the finding that few if any Upper Peninsula anglers regularly consume carp (West et al., 1993) . The impact of this unfounded assumption was significant since the available fish tissue sampling data showed that carp consistently contained the highest concentrations of PCBs of all fish species sampled in Michigan. For example, the tissue concentration for carp used in the Manistique BHHRA was 6.5 mg/kg; but the walleye tissue concentration was only 0.34 mg/kg.
- It was assumed that subsistence anglers obtained 50% (average exposure scenario) or 100% (high-end scenario) of their fish from Manistique Harbor. This was unlikely given the demographics of the population and the difficulty associated with fishing from the banks of the Harbor. Manistique Harbor is small, the banks are bulkheaded, and better and more accessible fishing areas on Lake Michigan are readily available. It was also assumed that the anglers consumed fish from the Harbor 365 days a year. Since the Harbor freezes over in the winter, this assumes that a substantial amount of fish is caught, saved, and consumed over the winter. An informal survey of the resident community could not identify any individuals engaged in this level of fishing and consuming fish from the Harbor.

Consideration of more reasonable and scientifically-based exposure assumptions and toxicity factors would have demonstrated that the surface sediment concentrations of PCBs in the Harbor did not represent a significant risk to the local populations. One must question the benefit to society (locally and nationally) of remediating a harbor to PCB fish tissue levels of less than 0.5 mg/kg (as in the walleye) and average surface sediment concentrations basin wide (56 acres) of 5.2 mg/kg at the cost of over $48 million.

EPA's Recent Increase in the Default Assumption for Adult Soil Ingestion Rate

EPA recently increased its default assumption for adult soil ingestion rate from 50 mg/day to 100 mg/day (EPA, 2001c; EPA; 2002b). As justification for this change, the Agency cites its Risk Assessment Guidance for Superfund, Volume I: Human Health Evaluation Manual, Supplemental Guidance: Standard Default Exposure Factors (EPA,1991). This guidance relies on Calabrese et al. (1990) for the 100 mg/day figure. EPA's Exposure Factors Handbook (EPA, 1997b), on the other hand, continues to recommend an adult soil ingestion rate of 50 mg/day. The Exposure Factors Handbook value is also based primarily on Calabrese et al. (1990).

There is no basis for EPA's increase in the adult default soil ingestion rate or for the Agency's changing its mind on how to interpret Calabrese et al.(1990). The Exposure Factors Handbook accurately cites Calabrese et al. (1990) as having found a soil ingestion range of 30 to 100 mg/day and supporting a "reasonable central estimate of adult soil ingestion" of 50 mg/day. Be that as it may, the most recent work on this subject by Calabrese et al. (1997) and Stanek et al. (1997) supports an adult soil ingestion range of 20 to 40 mg/day. The authors of Stanek et al.(1997) also highlight many significant improvements over their previous work (i.e., Calabrese et al., 1990), supporting the use of the 1997 ingestion rates for risk assessment purposes. Thus, there is no scientific basis for use of a default soil consumption rate of 100 mg/day.

Refusal to Alter Construction Worker Soil Ingestion Rate

Historically, EPA and state regulatory agencies have used a soil consumption rate of 480 mg/day in assessing construction worker exposure to soil contaminants through the soil ingestion exposure route. Although EPA Headquarters has determined that this factor is excessive, Headquarters has to date not published guidance encouraging the EPA Regions and the states to use a more realistic value.

The soil ingestion value of 480 mg/day is based on Hawley (1985). The Hawley (1985) estimates of soil consumption rates are based not on empirical data, but rather on various assumptions about the extent to which soil/dust adheres to hands, hand-to-mouth behavior, and frequencies of indoor and outdoor activities. Hawley (1985) stated that his estimates of soil ingestion were subject to substantial uncertainty. EPA has stated that the Hawley (1985) estimates must be considered "conjectural" due to the lack of supporting measurements (EPA, 1997b).

To derive soil ingestion rate estimates, Hawley (1985) assumed that an adult, while engaged in yard work or other physical activity such as construction excavation, would incidentally ingest half of the soil that could coat the inside surfaces of his fingers and thumbs on both hands twice per day. He further assumed that soil would adhere to the skin at a rate of 3.5 milligrams of soil per square centimeter of skin surface ($mg/cm^2$). This estimated loading or adherence factor was based an approximation of both the density of the soil and the thickness of a layer of soil that might adhere to the hands of an individual in contact with the ground.

Sheppard (1995) showed that the Hawley (1985) estimate were excessive. Sheppard (1995) demonstrated that the soil loading assumption of 3.5 $mg/cm^2$ for the arms and hands would result in a very high and conspicuous soil load. Sheppard reported that a load of less than 1 $mg/cm^2$ was more reasonable because a load greater than 1 $mg/cm^2$ would be highly noticeable and would deter hand-to-mouth contact. Sheppard (1995) also noted that Hawley (1985) did not account for the fact that individuals with substantial amounts of soil on their hands would be unlikely to pick up food or put their hands in their mouths before washing or wiping their hands.

Recently, new data on soil adherence have been published. As reported by EPA (1997b), Kissel et al. (1996) and Holmes et al. (1996) directly measured the amount of soil that adheres to skin surfaces during a variety of occupational and recreational activities. These studies indicated that the amount of soil that adheres to the skin depends on the type of activity performed and the body parts that come into contact with the soil. As one would expect, soil adherence to the skin appears to be greatest during outdoor activities such as farming and gardening, and more soil/dust tends to adhere to the hands than to other areas of the body.

Using the data provided by Holmes et al. (1996), EPA's dermal workgroup derived average (geometric mean) and high-end (95th percentile) adherence rates of 0.24 $mg/cm^2$ and 0.468 $mg/cm^2$, respectively, for the hands of construction workers and recommended that these values be used in risk assessment (EPA, 1997b; EPA, 2001f). Even the high-end adherence factor

(0.468 mg/cm$^2$) measured by Holmes et al (1996) is considerably lower than Hawley's estimate of 3.5 mg/cm$^2$.

If one uses EPA's (1999c; 2001f) average (0.24 mg/cm$^2$) and high-end (0.468 mg/cm$^2$) soil adherence values for the hands of construction workers in place of Hawley's assumed adherence value of 3.5 mg/cm$^2$, but retains all of Hawley's other exposure assumptions, the resulting construction worker soil ingestion rate ranges from 33 mg/day (average) to 64 mg/day (high-end). Thus, a conservative soil ingestion rate for a construction worker is 64 mg of soil per day, not the value of 480 mg/day which is still embraced by the EPA regions.

Continued Use of Excessive Dermal Absorption Rate for PCBs

In evaluating dermal absorption of a chemical in soil, EPA selects a dermal absorption factor to estimate the fraction of the chemical in the soil adhering to the skin that will actually be absorbed. For PCBs, EPA (2001f) assumes a 14 percent absorption factor based on a study by Wester et al. (1993). This absorption factor likely overestimates the fraction of PCBs that are absorbed due to the following limitations with the study.

- The Wester et al. study evaluated dermal uptake from larger grained sandy soil that had an organic carbon content much lower than that typically found in soils and sediments at PCB-contaminated sites. As demonstrated by Roy et al. (1990), higher levels of organic carbon in soils substantially decrease the bioavailability of PCBs for dermal absorption.
- The study methodology did not mimic chemical mixtures or conditions of dermal exposure that would be expected to occur during and after actual exposures.
- A number of studies have shown that a significant fraction of PCBs that have been in soil or sediment for a considerable period of time become tightly bound to the soil or sediment and desorb quite slowly, thus reducing their bioavailability. Wester et al., however, evaluated absorption of freshly spiked PCBs, an approach that does not emulate the fate of aged PCBs in site soils.
- Studies have shown that dermal uptake by monkeys is greater than uptake through human skin and that permeability of abdominal skin (as was tested by Wester et al.) is much greater than permeability of the extremities – the skin areas most likely to be in contact with site soils and sediments.

These limitations indicate that the 14 percent dermal absorption factor derived from Wester et al. (1993) likely overestimates the degree of dermal absorption of PCBs. General Electric sponsored a study to evaluate several aspects of the Wester et al. (1993) study in order to estimate PCB dermal absorption for application in the risk assessment for the Housatonic River site. This study was conducted by Huntingdon Life Sciences using Rhesus monkeys as test animals and soil taken from the Housatonic River floodplain that was spiked with Aroclor 1260, the PCB mixture most common to the Housatonic River site. The floodplain soil had an organic carbon content of 5-6 percent, which is typical of most soil and is in contrast to the 0.9 percent organic carbon content in the soil used by Wester et al. Because Wester et al. used soil that had been freshly spiked with PCBs, the Huntington study evaluated the relative rate of PCB absorption from freshly spiked PCB soil versus that from PCB-containing soil that had been aged to simulate weathered PCB soil. Finally, since the 24-hour exposure period evaluated by Wester et al. seems likely to have overestimated the period that humans would be dermally exposed to PCB-containing soil before washing, the Huntington study included a 12-hour dermal exposure period as well as 24-hour exposures. All other aspects of the Huntington study were similar to those used by Wester et al.

Using the same procedure as Wester et al. to calculate dermal absorption rates, the calculated mean dermal absorption rates for PCBs from soil in the Huntington study were:

Group exposed for 12 hours to aged PCBs in soil: 3.43 percent
Group exposed for 24 hours to freshly spiked PCBs in soil: 4.07 percent
Group exposed for 24 hours to aged PCBs in soil: 4.26 percent

As the results show, the use of the default 14 percent dermal absorption factor is not appropriate for a risk assessment of the Housatonic River; rather a dermal absorption factor of approximately 4 percent would be recommended based on site-specific data. Moreover, 4 percent would be a more appropriate factor at any site where the organic carbon content of the soil is similar to that in the Huntingdon study.

To date, EPA has not accepted the dermal absorption factor of 4 percent and still relies on its default value of 14 percent.

EPA Failure to Perform Probabilistic Risk Assessments

The evaluation of variability and uncertainty is an important component of the risk characterization task of risk assessment. As stated in the 1995 Risk Characterization memorandum from Administrator Carol Browner (EPA, 1995b):

> [W]e must fully, openly, and clearly characterize risks. In doing so, we will disclose the scientific analyses, uncertainties, assumptions, and science policies which underlie our decisions . . . . There is value in sharing with others the complexities and challenges we face in making decisions in the face of uncertainty.

EPA's Risk Assessment Guidance for Superfund (RAGS) Volume III: Part A (EPA, 2001a) provides technical guidance on the application of probabilistic risk assessment (PRA) methods to human health and ecological risk assessments in the Superfund program. The guidance focuses on Monte Carlo analysis (MCA) as a method of quantifying variability and uncertainty in risk. In addition, the 1997 EPA Policy for Use of Probabilistic Analysis in Risk Assessment (EPA, 1997c) states:

> It is the policy of the U.S. Environmental Protection Agency that such probabilistic analysis techniques as Monte Carlo analysis, given adequate supporting data and credible assumptions, can be viable statistical tools for analyzing variability and uncertainty in risk assessments.

According to EPA (2001a), the decision to use probabilistic analysis is

> site-specific and is based on the complexity of the problems at the site, the quality and extent of site-specific data, and the likely utility of the result. If the additional information provided from a PRA is unlikely to affect the risk management decision, then it may not be prudent to proceed with a PRA. However, if there is a clear value added from performing a PRA, then the use of PRA as a risk assessment tool generally should be considered despite the additional resources that may be needed.

EPA (2001a) endorses advanced modeling approaches for characterizing variability and uncertainty. According to EPA (2001a), an example of a more advanced approach is Microexposure Event Analysis (MEE):

> Where information is available to characterize variability on a smaller time scale than life-time, an alternative expression of dose that accommodates such variability may be desirable. Daily activity patterns, food intake, soil ingestion and other behavioral factors are measured in a time period of less than a year. The extrapolation of these short term results to the chronic exposure situation is a source of uncertainty. Exposure events are real but

> unknowable, whereas data regarding the nature and magnitude of these events is known but its application to a real world situation is uncertain. Microexposure event analysis (MEE) attempts to explicitly quantify this uncertainty. MEE modeling provides an alternative to the standard time-averaging approach. In the MEE approach, long term intake is viewed as the sum of individual exposure events. Implementing the MEE approach in a PRA requires dividing the exposure duration into short epochs, or time steps, within which the values assigned to exposure variables remain constant, but are allowed to vary from one time step to the next.

In other words, MEE captures temporal changes in inter-individual variation (Simon, 1999).

The theory and methodology of the MEE model are documented in the literature (Harrington et al., 1995; Price et al., 1996; Keenan et al., 1996; Simon, 1999). In brief, an individual's total exposure to a contaminant is calculated by summing the doses received during many individual exposure events. Each individual event is simulated using information specific to the time and location of the exposure events. The number of events and sequence in which they occur in the person's life can be simulated based upon information about an individual's short- and long-term behavior. This approach avoids the difficulty inherent in conventional Monte Carlo modeling where unrealistic exposures may be projected due to coincidental selection of the upper percentiles of two or more input distributions.

Although EPA's guidance endorses PRA, including Monte Carlo analysis and MEE, EPA often EPA views probabilistic analysis as a means to support point estimate risks, rather than as a way to more accurately characterize risks. As examples, two prominent Superfund sites involving sizeable river systems with PCB-contaminated sediments – the Upper Hudson and Fox Rivers -- are discussed below.

Upper Hudson River Probabilistic HHRA

EPA's probabilistic model for the Upper Hudson River included deficiencies in both the model design and documentation of the assessment. The design of the HHRA model forced EPA to assume that anglers consumed unrealistic amounts of fish harvested from the same locations, cooked in the same fashion, and composed of the same mixture of species every year for more than 30 years. The model did not account for the way in which people's behavior would vary over time, nor did the HHRA account for declining concentrations in fish tissue PCB levels in the future.

Had EPA followed its own guidance and used an MEE model, it would have generated more realistic estimates of exposure from ingesting Upper Hudson River fish. Exposures to Hudson River anglers should have been modeled as a series of separate exposure events that occur over time, taking into consideration temporal changes in fish tissue concentrations and angler behaviors. Furthermore, had EPA used the MEE model to compare the benefits of several remedial alternatives at reducing risks to the hypothetical fish consuming angler, it would have demonstrated that dredging produces no additional risk reduction compared to source control and that source control achieves acceptable PCB concentrations in fish for the average Upper Hudson River angler ten years sooner than does dredging in 29 of the 40 miles of the Site. Moreover, the MEE model demonstrated that source control achieves lower risks to human health (both cancer and non-cancer) than dredging in 34 of the 40 miles of the Site. EPA ignored the results of this analysis and issued a ROD for the Upper Hudson River which includes a dredging project of unprecedented scale which is projected to cost well over $500,000,000.

Fox River Probabilistic HHRA

EPA Region 5 and Wisconsin Department of Natural Resources (WDNR) conducted a HHRA that relied principally on a point estimate or deterministic approach in arriving at estimates of cancer and noncancer risk from consuming fish from the Lower Fox River. Although the EPA/WDNR HHRA used certain probabilistic methods as part of a sensitivity analysis, the HHRA did not include a true probabilistic risk assessment. As noted earlier in these comments, many of the input assumptions used in the EPA/WDNR HHRA, especially those relating to fish consumption rates, PCB fish tissue concentrations, and population mobility, were flawed or based on outdated information. Consequently, due to the multiplicative nature of deterministic assessments, the HHRA results overestimated risk by up to several orders of magnitude.

The Fox River Group companies (FRG) prepared an alternative Human Health Risk Assessment of the Lower Fox River and Green Bay (AMEC, 2002a). The starting point for the FRG's HHRA was the use of reliable scientific data from Fox River fish, sediments, and water that reflect current conditions and historical trends. The risk assessment incorporated a large media sampling database, Wisconsin fish consumption data, age- and region-specific data on human mobility, and state-of-the-art fate and transport, food web, and risk assessment models. In accordance with EPA (2001a) guidance, the FRG conducted an advanced Microexposure Event (MEE) probabilistic risk assessment because such an analysis adds value whenever screening risk estimates are above levels of concern and when the costs of remediation are high. Output from the MEE model showed that estimated risks were lower than the risks calculated in the EPA/WDNR HHRA by at least an order of magnitude, and in some cases, by as much as two orders of magnitude. Furthermore, when the MEE model was used to compare various remedial alternatives, it demonstrated that the proposed massive dredging remedy would offer no measurable benefit at reducing human health risks to anglers who fish the Fox River or Green Bay.

B. Toxicity Assessment

Toxicity assessment begins with a review of all relevant studies regarding the toxicity of the chemical at issue through all relevant routes of exposure (e.g., oral, dermal or inhalation). The next step is determining the critical effect – generally, the health effect caused by the chemical which occurs at a dose lower than the doses that cause any other health effects that the chemical may have. Then, a decision is made regarding the study data which will be used to quantify the toxicity of the chemical. If the chemical is a noncarcinogen, a NOAEL, LOAEL or Benchmark Dose Lower Limit (BMDL) is determined from the study data. The LOAEL, NOAEL or BMDL is, if necessary, converted from a measure of concentration (e.g., µg/L of blood) to a measure of dose (e.g., µg/kg body weight/day). Finally, the LOAEL, NOAEL or BMDL is divided by one or more uncertainty factors to yield the RfD, the ultimate product of the toxicity assessment.

If the chemical is a carcinogen, a model is used to derive a cancer slope factor (CSF) from the tumor count data from the chosen study. Essentially, a so-called "best-fit" line is drawn between the responses observed in an animal bioassay and that line is then extrapolated under a linear low-dose response assumption in order to predict the dose that would be anticipated to produce either a 10 percent ($ED_{10}$) or a 1 percent ($ED_{01}$) response rate in the population of test animals. Next, the linear low-dose response model is used to predict the statistical 95 percent lower confidence bound of the $ED_{10}$ or $ED_{01}$ (the $LED_{10}$ or $LED_{01}$, respectively). Finally, a straight line, linear low-dose extrapolation is performed between either the $LED_{10}$ or $LED_{01}$ and zero, and the slope of this line is the cancer slope factor or CSF.

Toxicity assessments are typically not performed by EPA in the course of risk assessments when EPA's Integrated Risk Information System database (IRIS, 2003) contains a current RfD or CSF for the chemical at issue. However, EPA risk assessors have been advised to consider all available data in the course of risk assessments as well as to perform a toxicity assessment when new data are available that were not originally considered in developing the IRIS RfD or CSF (EPA, 1993).

EPA toxicity assessments are often over-conservative for several reasons. For carcinogens, a pervasive problem has been use of a linear multi-stage (LMS) model to estimate low-dose cancer risk from high-dose animal studies. Although EPA guidance does not require use of this model where dose-response and/or mechanistic information exist, the Agency has often been unwilling in practice to depart from use of the LMS model. In the case of non-carcinogens, the most prevalent problem is the magnitude and number of uncertainty factors used to derive an RfD from study dose-response data. Another problem arises from the Agency's refusal to abandon misconceptions regarding the hazards posed by a chemical even in the presence of long-term human data showing that the chemical does not cause adverse health effects at doses that EPA predicts to be harmful. Some examples of these problems, all of which result in overestimates of chemical toxicity, follow.

EPA Cancer Risk Assessment Procedures

The Executive Summary to these comments quotes an EPA guidance document for the proposition that EPA risk assessments typically overpredict risk:

> To account for these uncertainties and to acknowledge gaps in science, we build in safety factors in the risk estimates which tend to overestimate what we believe to be the actual risk. Where there is uncertainty or where our information is incomplete, we make assumptions that tend to overestimate the risks as a way to insure the public health is protected.

EPA (2000a). Nowhere is this more likely than in the area of cancer risk assessment. EPA's 1986 cancer risk guidelines states that:

> It should be emphasized that the linearized multistage procedure leads to a plausible upper limit to the risk that is consistent with some proposed mechanisms of carcinogenesis. Such an estimate, however, does not necessarily give a realistic prediction of the risk. The true value of the risk is unknown, and may be as low as zero.

EPA (1986a).

Over the last several years, EPA has been in the process of revising its cancer risk assessment guidelines. Although the revisions, including the 2003 draft final guidelines (EPA, 2003a), have sought to bring more precision to the process of assessing the human cancer risk of chemicals, the processes set forth in the guidelines continue to inject a high degree of conservatism into carcinogenicity assessment. In fact, although EPA continues to admit that its carcinogen risk assessment procedures, particularly use of the linearized multistage (LMS) model, may predict risk when none exist, EPA is actually playing-down the problem. There are so many conservative aspects of EPA's cancer risk assessment procedures that EPA cancer assessments typically predict substantial risk when none exists. The following provides a brief summary of seven of EPA's cancer assessment procedures that combine to grossly exaggerate cancer risk from exposure to chemicals:

- Although the use of the LMS as a default, in itself, tends to overstate risk in virtually all cases, EPA compounds the problem by stating its preference for a default "Lower Limit on Effective Dose" (LED10), defined as the "lower 95% limit on a dose that is estimated to cause a 10% response" (EPA, 2003a). According to EPA, the LED10 is a "protective" level to account for experimental variability. Although the LED 10 is certainly protective, the EPA Science Advisory Board (SAB) (SAB, 1997) and the American Industrial Health Council (American Industrial Health Council, 1999) have recognized that using the LED 10 as the departure point in carcinogen risk assessment injects a layer of undue conservatism in what should be a scientific, not a public policy, exercise. Accordingly, these groups have urged EPA to use the central estimate "Effective Dose (ED)" (ED10) as the point of departure in an effort to most accurately characterize risk. EPA disagrees, arguing that the

ED10 is appropriate only for use in ranking the relative hazard/potency of agents for priority setting. The Council submits that this position is driven by nothing other than an effort to inject conservatism into the risk assessment process instead of leaving public policy judgments to the risk management phase.

- EPA guidance allows departure from the LMS when sufficient mode of action data are available: "When adequate data on [mode of action] show that linearity is not plausible, and provide sufficient evidence to support a nonlinear [mode of action] for the general population and any subpopulations of concern, the default changes to a different approach – a reference dose/reference concentration – that assumes that nonlinearity is more reasonable" (EPA, 2003a). Note that EPA's statement contains a significant qualifier that will very rarely be met – the LMS may be abandoned only when a nonlinear mode of action is supported for both the general population and any "subpopulations" that EPA may deem to be "of concern." Moreover, EPA again insists that the point of departure be the conservative LED 10, not the central tendency ED 10 (EPA, 2003a). Finally, EPA states that "the point of departure mostly will be from . . . precursor response data, for example hormone levels of mitogenic effects rather than tumor incidence data" (EPA, 2003a). This means that EPA will predict carcinogenicity from possible precancer effects, rather than from actual tumor data. Thus, EPA will allow risk assessors to depart from the default assumption of the ultraconservative LMS – but only if they then inject additional levels of conservatism into their risk assessment.
- In its treatment of epidemiological data, EPA states that its default position is as follows: "When cancer effects in exposed humans are attributed to exposure to an exogenous agent, the default assumption is that such data are predictive of cancer in any other exposed human population" (EPA, 2003a). This assumption seems fair. But EPA also states: "When cancer effects are not found in an exposed human population, this information by itself is not generally sufficient to conclude that the agent poses no carcinogenic hazard to this or other populations of potentially exposed humans, including susceptible subpopulations or life stages" (EPA, 2003a) (emphasis added). In part, this statement also seems fair – for example, it would not necessarily be appropriate to conclude from a negative cancer occupational exposure study that the substance in question does not pose carcinogenic risks to infants.[10] But EPA is saying more than that – the quoted language states that when cancer effects are not found in an exposed human population, this information may not be sufficient to conclude that the chemical does not pose a threat to that very population. In other words, negative epidemiological studies will generally be ignored by the Agency.
- When no adequate human data are available, EPA's default position is that "positive effects in animal cancer studies indicate that the agent under study can have carcinogenic potential in humans." Note that this default is applied in conjunction with the default position concerning negative epidemiological studies addressed in the preceding paragraph. The result is that as little as a single rodent study indicating that a chemical is a rodent carcinogen at high doses will be deemed to trump several negative human epidemiological studies. This is not unbiased, scientific risk assessment seeking to accurately and precisely estimate human health risks. Rather, it is a public policy position masquerading as a risk assessment default

[10] But, of course, there would be no presumption that the substance did pose risks to infants.

procedure. Note that EPA admits as much in the 2003 draft cancer guidelines, referring to the animal study default assumption as a "public-health conservative policy," while acknowledging "the extent to which animal studies may yield false positive indications for humans is a matter of scientific debate" (EPA, 2003a).

- Another EPA default assumption in the case of animal bioassays is that "effects seen at the highest dose tested are appropriate for assessment," although it is "necessary that the experimental conditions be scrutinized." As EPA acknowledges, use of the "maximum tolerated dose" to project effects at low doses raises questions of whether tumorigenic effects seen at high doses are merely the result of cell mortality and regeneration rather than of the substance's inherent carcinogenicity.
- In the case of negative animal bioassays, EPA's default position is as follows: "When cancer effects are not found in well conducted animal cancer studies in two or more appropriate species and other information does not support the carcinogenic potential of the agent, these data provide a basis for concluding that the agent is not likely to possess human carcinogenic potential, in the absence of human data to the contrary" (EPA, 2003a). But, as with negative epidemiological data, EPA hedges on this default, citing its "limitations" and stipulating that because standard bioassays have limited power to detect cancer effects, other information should be considered (e.g., absence of mutagenic or carcinogenic activity among structural analogues) (EPA, 2003a). Again, instead of assessing the weight of the evidence and relying on the result of that assessment, EPA urges its risk assessors to continue to look for any scintilla of evidence that a chemical might possibly have carcinioenic effects and be ready and willing to abandon the weight of the evidence based on that evidence.
- Another EPA default position applied to animal bioassays is that "target organ concordance is not a prerequisite for evaluating the implications of animal study results for humans." This approach is unduly conservative because it calls for extrapolating animal response to humans even in the presence of direct evidence that the response does not occur in humans.

Increase in the IUR for 1,3-Butadiene

In November 2002, EPA updated its IRIS Carcinogenicity Assessment for Lifetime Exposure and Chronic Health Hazard Assessment for Noncarcinogenic Effects for 1,3-butadiene. The support document for this update was EPA's Health Assessment of 1,3-Butadiene (EPA, 2002c). EPA based its cancer assessment on an epidemiology study (Delzell et al., 1996) in which 1,3-butadiene exposure was associated with leukemia in polymer workers exposed to the chemical during styrene-butadiene rubber (SBR) production. Delzell et al. (1996) was a high quality study of workers that showed only a weak association between leukemia and workplace exposures that often were in the range of 10 parts per million – or 1,000,000-fold above the level EPA estimates poses a one in a million cancer risk.

The inhalation unit risk (IUR) represents an estimate of the lifetime extra cancer risk associated with a unit of 1,3-butadiene concentration in ambient air. The new IUR estimate for 1,3-butadiene is $3 \times 10^{-5}$ $(\mu g/m^3)^{-1}$, which can also be expressed as 0.08/ppm. The corresponding concentration in ambient air that is estimated to pose a one in a million lifetime excess cancer risk is 0.01 part per billion (ppb) (0.03 $\mu g/m^3$).

The new 1,3-butadiene IUR, which is based on a human study, is less stringent than the previous IRIS IUR for this chemical, which was based on an animal study. However, the new IUR is more stringent than EPA's original draft IUR for 1,3-butadiene, which was based on the human study. To understand the changes made by EPA to the IUR for 1,3-butadiene it is helpful to trace the history of the update. This history illustrates two points: (i) how difficult it is for EPA institutionally to make a cancer potency estimate less stringent, even when strong scientific information supports such a decision; and (ii) how EPA's risk assessment methodology can result in an unrealistic estimate of risk if the cumulative impact of the various "health protective" decisions is not carefully evaluated.

Before 1998, the IUR for 1,3-butadiene was 0.7/ppm ($2.8 \times 10^{-4}$ $(\mu g/m^3)^{-1}$), based on tumor data from a mouse bioassay (NTP, 1984). In 1998, EPA issued a draft Health Assessment Document for 1,3-butadiene that proposed a cancer potency estimate of 0.009/ppm (EPA, 1998b). The corresponding level in ambient air estimated to pose a one in a million cancer risk was 0.1 ppb. EPA stated that it had "relatively high" confidence in the excess cancer risk estimate because it was based on "a large, high-quality epidemiologic study [Delzell et al., 1996] in which 1,3-butadiene exposures were estimated for each individual a priori to conducting the exposure-response analysis" (EPA, 1998b). EPA stated further that"[i]t is virtually unprecedented to have such a comprehensive exposure assessment for individual workers in such a large occupational epidemiologic study."

In 1999, EPA made two changes to its cancer potency estimate for 1,3-butadiene in response to recommendations by the EPA Science Advisory Board (SAB) Environmental Health Committee (EHC) (EPA, 1999d). The changes reduced the cancer potency estimate for 1,3-butadiene to 0.0046/ppm, or by about one-half. The corresponding estimate of a level in ambient air that would pose a one in a million excess cancer risk would be 0.2 ppb. This information was

supplied to EPA's Emissions Standards Division for use in certain ongoing regulatory initiatives. EPA advised the Emissions Standards Division as follows:

> The SAB also noted, and we concur, that since the mechanism of action is very different in humans as compared to the mechanism of action in mice, the earlier risk estimate (i.e., IRIS estimate based on mouse tumor data) is not an appropriate basis from which to extrapolate the human risk, hence making the existing IRIS value scientifically unsupportable. The prudent approach for current analysis would be to recognize the Agency's new recalculated 'draft' cancer risk estimate from the current assessment.

(EPA, 1999d). EPA stated further, "This estimate will be presented in our final assessment which is expected to be finished this fall."

Like all EPA cancer risk assessments, the 1999 cancer potency estimate was designed to be an "upper bound" estimate of the potential human cancer risk, with the recognition that the true risk at low exposures could be much lower and could even be zero. There was no scientific reason to believe the 1999 cancer potency estimate was not fully protective of the general population that might be exposed to low levels of 1,3-butadiene in ambient air.

Nevertheless, because the 1999 cancer potency estimate involved lowering EPA's estimate of the potential cancer risk from ambient exposures, it was heavily criticized by some parties. EPA responded to this criticism by extending its deliberations another three years, and finally produced in 2002 a 1,3-Butadiene Health Assessment that combines both human- and animal-based cancer potency estimates (EPA, 2002c). The results of this cancer risk estimate come much closer to the mouse-based risk assessment in IRIS that EPA had said was "not an appropriate basis from which to extrapolate the human risk"(EPA, 1999d).

EPA's deliberations from 1999 to 2002 did not produce a more scientifically defensible cancer risk estimate for butadiene. Rather, EPA's 2002 1,3-butadiene Heath Risk Estimate produced an overly conservative cancer potency estimate for the chemical by departing from normal EPA risk assessment practices, disregarding specific SAB recommendations, and failing to recognize that its numerous "health protective" choices were producing in the aggregate a scientifically implausible result. EPA's primary errors are summarized below:

- <u>EPA ignored SAB advice to adjust for the apparent role of peak exposures</u>. Many of the workers who were studied in Delzell et al. (1996) had very high "peak" exposures to 1,3-butadiene, defined in the study as exposures above 100 ppm. The SAB recommended that EPA exclude those exposures from its dose-response modeling: "In each dose group, adjustment for peak exposures reduced the leukemia risk substantially. Since butadiene exposures to the public will almost never approach the peak exposure range, a more appropriate model for risk would factor out the peak-exposure component" (SAB, 1998). EPA disregarded this advice.
- <u>EPA departed from its usual practice of using the maximum likelihood estimate (MLE) of risk when deriving a cancer risk estimate from human data</u>. In 1998 and 1999, EPA based its

calculations on the MLE of excess cancer risk, which is typical practice for human data, instead of the 95% upper confidence limit (UCL) typically used with animal data. EPA's main reason for use of the MLE in 1998 and 1999 was that "these estimates are based on human data from a large, well-conducted study" (EPA, 1998b, page 9-15). In the 2002 final assessment, EPA switched to the UCL, even though it acknowledged that it "has historically used MLEs for cancer risk estimates from human data rather than upper bounds as used with animal data." (EPA, 2002c, page 10-20) EPA used of the UCL was allegedly based on a "policy position expressed in the 1996 and 1999 proposed [cancer risk assessment] guidelines"(*Id*., page 10-21). However, there is no statement in either document that supports use of the UCL when cancer risk is estimated from human data.

- EPA did not use the model suggested by the SAB for estimating lifetime excess cancer risk in the general population. When estimating the excess cancer risk for the general population, EPA used cumulative lifetime exposure as the relevant measure of dose. The SAB urged instead consideration of a "window of exposure" model that had been used previously by the National Academy of Sciences to estimate lung cancer risk from radon. The SAB stated:

> Regarding the Delzell analysis of butadiene exposure vs. leukemia, … it is noted that 'excluding exposures within 20 years of death weakened and almost eliminated the relationship….' This indicates that in modeling lifetime risk, a model that assumes a limited effect time (i.e., that leukemia risk during a given year of age is affected largely by the butadiene exposures received during the previous, say, 20 years, and only slightly or not at all by more distant ones) should be considered. This 'window of exposure' model has precedents, e.g., lung cancer risk from radon has been modeled in this way in a National Academy of Sciences report ….

(SAB, 1998, page 38) The SAB stated further:

> If this model were considered for projecting lifetime risk, it would show appreciably less risk from chronic exposures than does the present one, which assumes an excess relative risk at, say, age 70 is an additive function of all the exposure accumulated in the previous 69 years.

(*Id*.) There is no scientific basis for believing that exposures to 1,3-butadiene have a significant impact on cancer risk 50, 60, 70 or 85 years later. The data from the Delzell et al. (1996) study and scientific understanding of cancer latency from human studies contradicts such an assumption in this case. EPA's standard approach of using cumulative lifetime dose exaggerates excess cancer risks later in life, and produces an inflated estimate of general population cancer risks. In the case of 1,3-butadiene, a high quality human study supported a different and more scientifically plausible "window of exposure" approach, yet EPA chose not to use that approach, and failed even to respond to the SAB's recommendation.

- EPA's final 2002 Health Assessment computed lifetime excess cancer risks up to age 85, instead of following the Agency's standard practice of calculating risks to age 70. In 1998, EPA calculated lifetime cancer risks up to age 85. The SAB recommended that EPA follow

its normal practice of calculating lifetime cancer risk up to age 70. EPA followed that recommendation in 1999, when it provided an updated cancer potency estimate to the Emissions Standards Division. As EPA explained in its memorandum, "[t]he SAB . . . noted the need to revise the calculations to account for . . . 70 years at risk instead of 85 years" (EPA, 1999d). Nevertheless, EPA's final 2002 assessment offers no explanation for switching back to the calculation based on 85 years. EPA's departure from its typical practice of using 70 years, without explanation, contravenes the core value of "consistency in core assumptions and science policies from case to case" (EPA, 1999b [Cancer Guidelines], page 5-2). Estimating cancer risks to age 85 years also adds to the overstatement of risk caused by EPA's use of lifetime cumulative exposure as the relevant measure of dose.

- EPA departed from its usual practice of basing estimates of lifetime excess cancer risk on general population mortality rates (as opposed to incidence rates). EPA typically derives its estimates of lifetime excess cancer risk for the general population by applying a calculated unit cancer risk estimate (based on human or animal data) to published data on background cancer mortality rates for the general population. EPA does not typically use cancer incidence rates for the general population. In 1998, EPA did not even discuss the possibility of relying on cancer incidence data, and simply took for granted that it would follow the Agency's normal practice of using mortality data. EPA's decision in the final Health Assessment Document to use incidence rates, instead of mortality rates, once again contravenes the core risk assessment value of consistency. No chemical-specific rationale for departing from the standard risk assessment practice was presented.

- EPA applied an extra adjustment factor of 2 to its cancer risk estimate without scientific justification. EPA stated that it applied an extra adjustment factor of 2 to its cancer risk estimate "to reflect evidence from rodent bioassays suggesting that extrapolating the excess risk of leukemia in a male-only occupational cohort may underestimate the total cancer risk from 1,3-butadiene exposure in the general population." (EPA, 2002c, page 10-21) No such factor was applied in the 1998 draft document, nor are we aware of any prior EPA cancer risk assessment where such an adjustment factor has been used.

  EPA asserted that there could be a small excess risk of lung cancer that was not observed in the worker study (EPA, 2002c, pages 10-15 and 10-22). EPA sought to bolster this speculation with a "crude" post-hoc power calculation. However, when making this power calculation, EPA used the MLE of excess lung cancer risk based on female mouse data, whereas elsewhere throughout the document EPA relied on 95% UCL values when deriving cancer risk estimates from animal data. Use of the MLE for the power calculation lowered the estimate of excess lung risk, and thus lowered the power of the study to detect that risk. Use of the MLE just for the "crude" power calculation, and not for any other purpose in the risk assessment document, rendered the entire exercise scientifically suspect.

  EPA's other reasons for adding an additional adjustment factor of 2 were no more persuasive. EPA in effect was combining a human-based cancer risk estimate with a mouse-based estimate, to more closely approximate the latter. EPA stated, "applying a two fold adjustment to the potency estimate of 0.04/ppm derived for leukemia incidence from the occupational epidemiologic study yields a cancer potency estimate of 0.08/ppm, which roughly corresponds to a combination of the human leukemia and mouse mammary gland tumor risk estimates, addressing the concern that the leukemia risk estimated from the

occupational data may underestimate total cancer risk for the general population, in particular females" (EPA, 2002c, page 11-3). Thus, EPA went back to relying on mouse data, despite its earlier recognition that mouse-human differences in mechanism of action were sufficiently great that previous mouse-based risk estimates were "not an appropriate basis from which to extrapolate the human risk" (EPA, 1999d). Moreover, the SAB had concluded that the rat provided a better model than the mouse for human risk assessment. (SAB, 1998, page 36)

- EPA failed to give adequate consideration to the cumulative impact of its many "health protective" choices. The preceding items identify several risk assessment decisions made by EPA that resulted in a substantial overstatement of likely human cancer risks from low level exposures to 1,3-butadiene. EPA's final risk estimate was 20-fold more conservative than the risk estimate it had provided to the Emissions Standards Division in 1999, and only 3-fold less stringent than the mouse-based risk estimate that EPA at that time said was "not an appropriate basis from which to extrapolate the human risk." EPA's Interim Cancer Risk Assessment Guidelines urge "reasonableness" as a core value, and EPA has stated that "common sense and reasonable application of assumptions and policies are essential to avoid unrealistic estimates of risk" (EPA, 1999b, page 5-2). In this case, EPA should have considered whether the collective impact of all of its risk assessment choices was scientifically reasonable. No such analysis was presented in the final health assessment document.
- Finally, because many of EPA's choices were made after the SAB peer review, there was no opportunity for peer review of whether EPA's final risk assessment choices, in the aggregate, were scientifically reasonable. There was no opportunity for external peer review to assess whether EPA's unusual risk assessment decisions (e.g., deciding to switch from the MLE to the 95% UCL, to apply an extra adjustment factor of 2, to ignore the role of peak exposures, to estimate lifetime risks based on 85 years instead of 70, and to use lifetime cumulative dose instead of a "windows of exposure" model as suggested by the SAB) produced a scientifically reasonable result.

The end result of EPA's assessment was an estimate that 10 parts per trillion of 1,3-butadiene in ambient air poses a one in a million cancer risk, even though workplace exposures that often were 1,000,000-fold higher produced evidence of only a weak association between exposure and leukemia, and even though that association almost disappears when "peak" exposures above 100 ppm are excluded. To infer from that data a cancer risk from exposure to 10 part per trillion of 1,3-butadiene in ambient air exceeds the bounds of scientific reasonableness. If there is any cancer risk to the general population from exposure to low levels of 1,3-butadiene in ambient air, it is likely that the upper bound of the estimated risk is well below what EPA presented in its Health Assessment Document.

The 1,3-butadiene cancer risk assessment will play a central role in risk assessments for several categories of stationary sources under the Clean Air Act, and also will be important to ongoing Agency assessments of toxic pollutants from mobile sources. In addition, the general public cannot be expected to understand the conservative nature of EPA's risk assessment. Thus, EPA's excessive conservatism can be expected to have real-world consequences.

## Revised RfD for Perchlorate

Ammonium perchlorate is manufactured for use as an oxidizer in solid rocket propellants for rockets, missiles and fireworks. Large volumes of perchlorate have been used in the aerospace and defense industries since the 1950s to fulfill contractual obligations to the Department of Defense (DOD) and NASA, as well as other government agencies. Perchlorate has been found in ground and surface water in 22 states and is pervasive in the Western United States (California, Nevada, Arizona, New Mexico, Texas, Utah and Arizona).

EPA developed an overall model for the perchlorate risk assessment based on perchlorate's mode of action, which is the competitive inhibition of active iodide uptake. In the thyroid gland, iodine is required to produce thyroid hormones. If perchlorate decreases iodine uptake in the thyroid gland, it can eventually lead to decreases in thyroid hormones. The condition of reduced thyroid hormones is called hypothyroidism. EPA has concern that if perchlorate causes maternal hypothyroidism, the developing fetus may be affected. EPA calls the inhibition of iodide uptake the key "event" that precedes hormone and thyroid changes, which in turn could precede neurodevelopmental effects.

In December 1998, EPA published a draft risk assessment recommending a RfD of 0.0009 mg/kg-day (drinking water equivalent of 32 ppb) based on a LOAEL of 0.1 mg/kg-day for thyroid histology and a composite uncertainty factor of 100. (EPA, 1998). An external peer review panel recommended further quality control on histologic endpoints and asserted that the proposed RfD was overly conservative.

In January, 2002, EPA published a draft toxicity assessment for perchlorate, recommending an RfD of 0.00003 mg/kg-day (EPA, 2002). This value equates to a drinking water level of 1 ppb. The draft RfD is substantially more conservative than those previously recommended by EPA (EPA, 1992; EPA, 1995).

There is no supportable scientific basis for the draft perchlorate RfD. To understand the deficiencies in EPA's development of the draft RfD for perchlorate, it is necessary to understand something about the chemistry of perchlorate and its mechanism of action in mammals.

Perchlorate is a negatively charged ion that has the same size and shape as iodide. The perchlorate anion is typically associated with the ammonium cation. Ammonium perchlorate looks, tastes and dissolves in water like table salt.

The thyroid takes in iodide, a necessary nutrient, at the sodium (Na+)-iodide (I-) symporter (NIS) (EPA, 2002). The thyroid uses iodide to make thyroid hormones T3 and T4, molecules that incorporate three or four iodine atoms respectively. The NIS is receptive to perchlorate to a somewhat larger extent than iodide. Thus, when perchlorate is present in the body it interferes with iodine uptake by the thyroid in a dose dependent manner. Inhibition of iodine uptake can be measured by giving a subject radioactive iodine and scanning the thyroid to see how much of the radioactive iodine is absorbed into the thyroid. Inhibition of Radioactive Iodine Uptake (RAIU inhibition) is the only direct effect of perchlorate on mammals.

If iodide uptake is sufficiently blocked for long enough, eventually the production of T3 and T4 will decrease. When it does, the brain releases more Thyroid Stimulating Hormone (TSH) to increase T3 and T4 production. In response to chronically elevated TSH levels, the thyroid gland enlarges (goiter). The most common cause of goiter is iodine deficiency. Iodine is intentionally added to food (mostly table salt) for this reason. There is no evidence of iodine deficiency in the United States.

Presumably, if the TSH concentration is high enough for a long enough time, the thyroid cells are continually stimulated to enlarge and divide. This can lead to mistakes in cell replication and can increase the risk of tumor formation. Blocking of T4 production leading to increased TSH production and thyroid growth is the only cancer mode of action for perchlorate. This has been demonstrated in the rat model but thyroid cancer is not elevated in countries with endemic goiter from iodine deficiency or other dietary goitrogens.

T3 and T4 are necessary to maintain normal metabolism in adults. A pattern of low T4 and high TSH is indicative of hypothyroidism. The most common cause of hypothyroidism world wide is an auto-immune problem where the immune system attacks the thyroid and shuts it down. The treatment for hypothyroidism is taking synthetic T4 in the form of a pill once a day.

T3 and T4 are also needed during fetal development, most importantly for normal development of the brain. In utero, the fetus obtains T3 and T4 from the mother beginning soon after conception. The fetus starts making its own T3 and T4 at the beginning of the second trimester, about the same time as T4 receptors appear in the brain. If a baby is born with a defect such that it cannot produce T3 and T4, it will be normal at birth but will then develop severe mental retardation and certain skeletal defects(cretinism) if he or she is not treated with T4 soon after birth..

In some cases, the thyroid gland is overactive. The most common cause of this is Graves Disease. Starting in the early 50's, perchlorate has been used as a medication to treat overactive thyroid glands. It is still used in Europe for this purpose.

Because perchlorate can reduce T4 production and because reduced T4 concentration can in some circumstances lead to thyroid cancer and defects in brain development in rats, EPA is concerned about the health implications of exposure to environmental levels of perchlorate. However, the available evidence indicates that perchlorate should not be expected to have any adverse health effects on humans at a dose that is at least 200 times higher than the RfD. We discuss the animal and human evidence in turn.

*Animal Evidence*

As noted above, the draft EPA RfD for perchlorate is based on animal studies in which a LOAEL of 0.01 mg/kg-day was observed (EPA, 2002). The point of departure was based principally on studies performed subsequent to the 1999 external peer review: the "effects study" (Argus Research Labs, 2001); a two-generation rat study (Argus 1999); and a mouse motor activity study performed by the U.S. Navy (Bekkedal 2000). Public comments as well as one member of

the 2002 external peer review panel pointed out that in all of the rodent studies relied upon by the EPA, the principle protein source in the animal diet was soy, a known goitrogen, and that recent studies by NTP and others have demonstrated a profound synergism between soy (isoflavones) and iodine deficiency.

In its "weight of the evidence" assessment, EPA considered several endpoints:

- Motor activity – Based on Bayesian hierarchical analysis of the Bekkedal (2000) (which was reported as a negative study by the authors), combined with a previous study (Argus 1998), EPA determined a LOAEL of 1 mg/kg-day.
- Thyroid tumors – Based on 3 tumors in 2 animals at 19 weeks in first F1 adults (Argus 1999), EPA compared the incidence of all thyroid tumors in NTP archives for rats at 2-year bioassay terminal sacrifice. Applying Bayesian analysis, EPA expressed a "concern" for in utero programming. One member of the 2002 external peer review panel accused EPA of "torturing the data."
- Thyroid histopathology – Based on histopathological findings of hyperplasia, EPA performed a BMDL analysis of the data from the "effects study." The lowest BMDL noted for hyperplasia was 1 mg/kg-day, which was assumed to be equivalent to a NOAEL.
- Thyroid hormones – EPA performed a BMDL analysis of thyroid hormone data (T4) from the "effects" study and determined the lowest BMDL of 0.01 mg/kg-day. Members of the 2002 external peer review panel pointed out that the "statistically significant" hormone changes were well within the normal range and not clinically significant.
- Brain Morphometry – EPA determined a LOAEL of 0.01 mg/kg-day based on statistically significant changes in the size of one brain structure (Argus, 2001). According to EPA, this "point of departure" was selected because when pregnant rats were given this dose during and after pregnancy, pups showed increased widths of some regions in the brain, particularly in the region called the corpus callosum. These effects were seen at only the middle doses given to pregnant rats, not in the control or highest doses. EPA calls this an inverted "U-shaped" dose-response curve. The only neurotoxicologist on the 2002 external peer review panel (Dr. Miki Aschner) reviewed the morphometry data in detail and asserted that the data are un-interpretable and any statistical manipulation of the data therefore meaningless. In comments to the EPA, other neurotoxicologists concluded that the rat brains were sliced in the wrong plane to appropriately evaluate the corpus callosum. EPA nevertheless used the controversial corpus callosum measurements as the "point of departure" for risk assessment (LOAEL 0.01 mg/kg-day).

The LOAEL of 0.01 mg/kg-day was converted to a human equivalent exposure using a physiologically-based pharmacokinetic (PBPK) model. A composite uncertainty factor of 300 was used:

- A three-fold factor for intraspecies variability was used due to the variability observed in the data and PBPK modeling.
- A full factor of ten was applied for LOAEL to NOAEL extrapolation.

- A three-fold factor for study duration was applied due to the concern for the biological importance of the statistically significant increase in thyroid tumors observed in a two-generation reproductive study.
- A three-fold factor was applied, apparently to account for database insufficiency, because "recent studies reinforced concern for [the immunotoxicity] endpoint."

(EPA, 2002d). Thus, the draft RfD is 0.01 x 0.85 / 300 = 0.00003 mg/kg-day.

*Human Evidence*

In 1952, perchlorate was determined to be more effective than other anions (including nitrate and thiocyanate) in inhibiting iodine uptake by the thyroid. (Stanbury et al., 1952; Wyngaarden et al., 1952, 1953). Subsequently, it has been used as a medication to treat hyperthyroidism associated with Grave's disease. Although more effective treatments for hyperthyroidism have been developed, perchlorate continues to be used medically in some circumstances. Adult dosages of potassium perchlorate of 200 – 900 mg/day produce clinical results.

Employees at Kerr-McGee's Henderson, NV facility were studied (Gibbs et al., 1998) as were employees of Ampac's Cedar City, UT facility (Lamm et al., 1999). Combined results of these studies and BMDL analyses (Crump, 1999) indicate no adverse thyroid or other health effects at dosages up to 0.7 mg/kg-day (DWEL of 25,000 ppb). These employees had worked in perchlorate manufacturing for an average of five years and a maximum of 20 years.

A human volunteer study was done at Boston University with 10mg/day dosing for two weeks and measurement of RAIU inhibition (Lawrence et al., 2000). The researchers noted 40% inhibition of radioactive iodine uptake but no changes in T4 or TSH levels. Although published in the journal *Thyroid*, EPA did not think that the data were useful due to QA/QC concerns.

A second human volunteer study was done in Oregon (Greer et al., 2002) with doses ranging from an equivalent of 200 ppb to 17,000 ppb perchlorate in water. The authors measured RAIU inhibition and thyroid hormones. There was no detectable RAIU inhibition at the low dose (a NOEL) and no hormone effects at the high dose despite 70% inhibition of RAIU. EPA helped design the study for PBPK modeling and used it only for calibration of the rodent data.

Perchlorate occurs naturally in northern Chile. Three coastal cities in northern Chile were located with 110, 6 and ND perchlorate ppb in drinking water. Approximately fifty first grade school children were studied in each city and neonatal screening data for a three year period from the same three cities were evaluated (Crump et al., 2000). There were no adverse thyroid or any other health differences attributable to life long exposure to perchlorate at 110 ppb. Serum and urine perchlorate levels among the school children drinking water with 110 ppb were consistent with the water level (27.5 kg child drinking 1 liter per day).

Thyroid hormone concentrations were compared for infants born to consumers of Las Vegas, Nevada, drinking water (which contains approximately12 ppb perchlorate) and infants born to consumers of Reno, Nevada, drinking water (no perchlorate detected in three published studies). No differences in neonatal thyroid screening T4 or TSH results (Li et al., 2000, Xiao et al., 2000)

or Medicaid data regarding prevalence of thyroid diseases or thyroid cancer were found (Li et al., 2001). There is no increase in neonatal hypothyroidism in southern California in zip codes associated with elevated perchlorate exposure (Lamm & Doemland, 1999).

An unpublished Masters thesis from Berkeley found a dose-related difference in neonatal thyroid hormones. (Schwartz, 2001). Faculty at the School of Public Health at Berkeley have recently performed a similar study and obtained negative results (Kelsh et al., 2003).

A study comparing neonatal screening data from Yuma, Arizona (6 ppb perchlorate in drinking water) and Flagstaff, Arizona (no detectable perchlorate in drinking water) found a slight difference in TSH (Brechner et al., 2000; Crump et al., 2001; Goodman 2001). The Yuma population has been revisited and the approximate half of the population with perchlorate exposure were found to have similar thyroid hormone levels as the approximate half of the population with no perchlorate exposure. Most of the difference in neonatal TSH levels between the Yuma and Flagstaff poputations was attributable to infant age at the time of testing.

EPA critiqued the human data in the 2002 draft risk assessment (EPA, 2002d). Other than a discussion of particle size of dust in the occupational studies (irrelevant because serum and urine levels confirmed absorption), nearly all of the critique of the human studies was by a single author (Park, 2001) from NIOSH who was apparently contracted by EPA.

* * *

The human studies provide a logical framework for deriving an RfD that is inherently protective and that renders uncertainty factors superfluous. Together, these studies show that for any adverse effect (e.g., clinical hypothyroidism) to occur, the dose of perchlorate would need to be high enough to cause significant (probably greater than 70%) inhibition of iodine uptake for several years (Lamm et al, 1999).

Based on Greer et al. (2002), the RfD should be 0.005 to 0.17 milligrams per kilogram of body weight per day, equivalent to 175 to 6,000 parts per billion in drinking water. The bases for the uncertainty factors that should be applied to the Greer study are as follows:

- LOAEL to NOAEL uncertainty factor: a value of less than 1 (e.g., 0.1 to 0.01) is used since the study provides an estimate of a no observed effect level (NOEL) instead of a no observed *adverse* effect level (NOAEL).
- Interspecies uncertainty factor: no extrapolation from animals to humans due to use of human data; therefore, 1 is appropriate.
- Intraspecies uncertainty factor: 3 to 10 for use of healthy adults in the study.
- Database uncertainty factor: the perchlorate database is extensive, including several studies in human populations, and its effects have been well characterized; therefore, 1 is appropriate.
- Subchronic to chronic uncertainty factor: due to the implausibility of chronic effects from perchlorate in the absence of acute effects, a factor of 1 is appropriate.

Proposed RfD for Acetone

EPA posted a draft Toxicological Review and draft IRIS summary for acetone on its web site on August 16, 2001, at the same time the documents were provided to external peer reviewers. EPA has proposed an oral RfD for acetone of 0.3 mg/kg/day. This value is more than 100-fold below normal endogenous production of acetone in healthy individuals. EPA reached this result by applying "standard" uncertainty factors that are not scientifically appropriate. EPA also understated the amount of information available to evaluate potential hazards from exposure to acetone, resulting in application of an additional uncertainty factor that further skews its RfD. EPA toxicity estimate for acetone is notably inconsistent with those of other scientists.

Acetone is naturally present throughout the human body as a result of its production during fatty acid catabolism. Infants and young children typically have higher acetone blood levels than adults due to their higher energy expenditures. Vigorous exercise, dieting, pregnancy, and lactation can also lead to normal fluctuations in the blood levels of acetone without any ill effect. The rate of acetone production in normal healthy adults is approximately 41 mg/kg/day (equivalent to approximately 2.9 g/day).[11] Thus, the proposed oral reference dose (RfD) for acetone of 0.3 mg/kg/day is more than 100-fold below normal endogenous production of acetone in healthy individuals. A daily dosage in the magnitude of the RfD is meaningless from a toxicological perspective, given endogenous production levels.

EPA's proposed RfD for acetone is also inconsistent with the toxicity assessments performed by other scientists and groups. The external co-author of the draft IRIS Toxicological Review, Dr. Forsyth of Oak Ridge National Laboratory, recommended an RfD for acetone of 3.0 mg/kg/day. In addition, the World Health Organization (WHO) has published an Environmental Health Criteria document for acetone that contains a recommended value of 9.0 mg/kg/day – a value that is 30-fold above EPA's recommendation (WHO, 1998). The WHO value is still below normal endogenous production rates in healthy individuals, but it is more scientifically plausible than the value proposed by EPA. The values differ from EPA's because both Dr. Forsyth and WHO use more scientifically defensible uncertainty factors than were applied by EPA.

Acetone exhibited very low toxicity in 90-day drinking water studies sponsored by the National Toxicology Program (NTP). Minimally toxic concentrations were estimated to be 20,000 ppm (1,700 mg/kg/day) for male rats, 20,000 ppm (4,858 mg/kg/day) for male mice, and 50,000 ppm (11,298 mg/kg/day) for female mice. No toxic effects were identified in female rats at the highest concentration of 50,000 ppm (3,100 mg/kg/day). NTP recommended against the conduct of chronic studies of acetone because "the prechronic studies only demonstrated a very mild toxic response at very high doses in rodents," and because of "the absence of any evidence supporting the carcinogenic potential for acetone" (NTP, 1989).[12] In other words, no chronic

[11] See G. A. Reichard et al., Plasma acetone metabolism in the fasting human. J. Clin. Invest. 63, 619-626 (1979), cited in Table 74.33 in Patty's Toxicology, Fifth Edition, Volume 6, Edited by Eula Bingham, Barbara Cohrssen, and Charles H. Powell.

[12] This recommendation was adopted by the Hazardous Waste Information Evaluation Subcommittee (HWIES) of

toxicity/oncogenicity study has been conducted for acetone because acetone exhibits such low toxicity that NTP has concluded chronic toxicity studies are not necessary.

In deriving the proposed RfD, EPA applied a combined total uncertainty factor of 3000 -- factors of 10 were applied for intraspecies extrapolation, subchronic-to-chronic extrapolation, and "database insufficiency", including the absence of a chronic study, and a factor of 3 was applied for interspecies variability. These factors are clearly excessive.

EPA did not provide a justification for applying an uncertainty factor for subchronic-to-chronic extrapolation, apart from noting that this is a "standard factor," and speculating that repeated exposures over an extended period of time "could lead to more pronounced effects." The available scientific data, however, do not support application of a factor of 10, and strongly contradict EPA's speculation. As noted above, NTP expressly concluded that the effects of acetone were so mild, at such high doses, that a chronic study was not necessary. Further, several published studies support the use of an uncertainty factor of less than 10 for the absence of a chronic study, particularly for substances like acetone that are readily metabolized and eliminated from the body. See, e.g., Dourson et al. (1996), Beck et al., (1992) and Nessel et al. (1995). Thus, the subchronic-to-chronic UF applied by EPA clearly is overly conservative in light of the available data on acetone.

The UF of 10 for database insufficiency also is excessive. EPA takes an overly compartmentalized approach, and fails to make use of inhalation studies of acetone (which also demonstrate low toxicity) when deriving the oral reference dose. In addition, isopropanol has been shown to be extensively metabolized to acetone and several TSCA guideline studies for this compound are available. The combination of inhalation data for acetone and numerous studies on isopropanol (including studies of chronic toxicity, neurotoxicity, developmental toxicity, reproductive toxicity and developmental neurotoxicity) are ample to fully evaluate the potential toxic effects of acetone, rendering a UF for database insufficiency completely unnecessary. EPA's draft IRIS summary drastically understates the amount of scientific information available to evaluate potential hazards from exposure to acetone. The draft IRIS summary gives a "low" rating to the database, but when acetone went through the OECD "Screening Information Data Set" (SIDS) review process, with the United States as the sponsor country, the SIDS Initial Assessment Report (SIAR) concluded that "[t]he human health and environmental effects of acetone have both been well studied" (EPA, 1999h). The SIAR reported that the most significant health effects of acetone are eye irritation and "an acute effect on the central nervous system," but noted that "high exposures are required and health hazards are slight," making acetone "a low priority for further work" (EPA, 1999h). Thus, the Council believes that no factor for database insufficiency is justified.[13]

---

the Public Health Service Committee to Coordinate Environmental Health and Related Programs. The recommendation of HWIES in turn was accepted by the Agency for Toxic Substances and Disease Registry (ATSDR), which had been considering proposing acetone for possible chronic toxicity testing. See 54 Fed. Reg. 42042 (October 13, 1989); 55 Fed. Reg. 34966 (August 27, 1990).

[13] The SIAR found that acetone has "low potential for systemic toxicity" and "showed minimal reproductive and developmental effects in animals exposed either by inhalation or via drinking water." The SIAR concluded that "acetone does not pose a neurotoxic, carcinogenic, or reproductive health hazard at the concentrations found anywhere in the environment." Indeed, the SIAR posits that the "ability of humans to naturally produce and dispose

An overly conservative approach to deriving an oral RfD can have significant negative consequences. By applying excessive uncertainty factors to materials of demonstrated low toxicity such as acetone, EPA makes it harder for prospective users of IRIS to make rational distinctions among compounds, and therefore harder to manage potential hazards and risks as effectively as possible. Further, when excessively conservative IRIS values are applied in particular regulatory settings, potential hazards may be identified where in fact none may reasonably be anticipated, and substantial resources may be wasted addressing scientifically implausible risks.

Moreover, the issues associated with the acetone RfD are compounded because, although the IRIS process has included an external peer review, EPA has refused to provide the external peer reviewers with the comments submitted by interested parties. IRIS documents are intended to serve as the starting point for risk assessments conducted by EPA program offices. EPA also expects its documents to be used by other federal and state agencies, and by other stakeholders and the general public. Given the breadth and importance of EPA's IRIS documents, peer reviewers should have access to all relevant information, including scientific input provided by interested parties (especially if it differs from what is contained in the draft documents). To command respect in regulatory and scientific communities, EPA's IRIS files must be the product of an open and unbiased process, where public comment is encouraged and all comments are given fair consideration. By not providing public comment to peer reviewers, the Agency undermines the validity of its findings.

---

of acetone may to a large degree explain its relatively low toxicity following external exposure to moderate amounts of the vapor or liquid." The SIAR was approved in its entirety by EPA scientists. Compared to the draft IRIS summary, the SIAR provides a more realistic and balanced assessment of the adequacy of existing data and acetone's potential health hazards.

Proposed RfD for Trichloroethylene

In developing an RfD for trichloroethylene (TCE), EPA applied, without adequate justification, several extremely conservative uncertainty factors. The result is an RfD that is one to two orders more stringent than necessary.

EPA identified several toxic effects associated with TCE exposure including liver, kidney, and developmental effects. It appears that the lowest doses are linked to changes in the liver weight to body weight ratio in both mice and rats. EPA (2001d) reports these doses in "human-equivalent terms" based on pharmacokinetic modeling performed by Clewell et al. (2000) and Barton and Clewell (2000). EPA selected a human-equivalent dose of 1 mg/kg-day as the point of departure, supported by liver toxicity observed in three studies (Tucker et al., 1982; Buben and O'Flaherty, 1985; Berman et al., 1995).

EPA characterized uncertainty associated with the reference values by applying several uncertainty factors to the "point-of-departure" dose. For the RfD, EPA (2001d) assigned a value of 50 for human variation and values of 3 for animal to human extrapolation, subchronic to chronic exposure, LOAEL to NOAEL extrapolation and background exposures, resulting in an overall uncertainty factor of 5000. This overall factor exceeds EPA's own maximum composite factor of 3000. Thus, EPA (2001d) limited the uncertainty factor to 3000, and applied it to the point of departure dose of 1 mg/kg-day to derive an oral RfD of $3 \times 10^{-4}$ mg/kg-day for TCE.

*Human Variation*

EPA (2001d) suggests the application of a 50-fold safety factor to account for human variation, based on a 3-fold factor to account for human pharmacodynamic differences and a 15 to 20-fold factor to account for uncertainties in the pharmacokinetic models applied to estimate human doses (this latter factor also subsumes the pharmacokinetic uncertainty associated with extrapolation from animals to man). EPA (2001d) justifies the 15 to 20-fold factor as the span between the 50th and 99th percentile of a range of potential values for two dose metrics arbitrarily modeled as log-normal.

Because 50% of the possible values for the dose metric are below the median, the 15 to 20-fold factor beyond the median may be characterized as a value that is applicable to, or too high for, 99% of the possible cases. Because of the (arbitrary) log-normal nature of the distribution, the "multiplier" on the median dose metric falls very quickly. Thus, the 95th percentile of the dose metric is more than 50% lower (i.e., if one selected the 95th percentile for determining the magnitude of the uncertainty factor, the value would be 7 to 8, rather than 15 to 20). The 90th percentile is lower still (i.e., the factor at this percentile would be approximately 4). As such, it would appear that this unprecedented high uncertainty factor proposed by EPA would provide very little additional protection;.

One must also use caution with a modeled distribution in that the extremes may be a statistical aberration rather than a duly conservative value from the upper range of a population of actual empirical values. By analogy, in dealing with uncertainty in the exposure assessment component

of the risk paradigm, EPA generally suggests a value with 90 to 98 percent confidence (EPA, 1992a). This guidance represents overall confidence, not the confidence derived from a single selected factor. Thus, attempting to achieve 99% confidence from a single uncertainty factor where other factors are also being used is excessive and inconsistent with typical regulatory practice. As such, it is suggested that an uncertainty factor to account for human pharmacokinetic variation be no greater than 4 (representing the 90th percentile on the dose metric as a multiple of the median) rather than 15 to 20. Multiplying this 4-fold human pharmocokinetic variation by an uncertainty factor of 3 for human pharmacodynamic variation results in an overall uncertainty factor for human variation of 10 when rounded to one significant digit. .

Furthermore, in their discussion of the intraspecies uncertainty factor, the TCE Reference Dose Technical Panel (EPA, 2001e) reported that Renwick and Lazarus (1998) demonstrated that an uncertainty factor of 10 accounted for "variability in both kinetics and dynamics in the vast majority of the population (>99%)."

*Subchronic to Chronic Dosing*

EPA (2001d) applied an uncertainty factor of 3 to account for subchronic to chronic exposure. EPA mischaracterized the studies providing a point of departure for liver endpoints as "subchronic." Tucker et al. (1982) exposed animals for 6 months. This is well in excess of rodent dosing periods typically characterized as "subchronic."

The definition of subchronic in the IRIS glossary is 10% of an animal's lifetime, which would be approximately 90 days. The EPA Office of Prevention, Pesticides, and Toxic Substances, OPPTS Protocol 870-3100, also characterizes a 90-day testing protocol as a "subchronic" test. And, the Reference Dose Technical Panel (EPA, 2001e) proposes the following definition for chronic exposure when establishing a chronic reference value: "repeated exposure by the oral, dermal or inhalation route for more than approximately 10% of the life span in humans." Furthermore, standard toxicology references typically characterize chronic dosing as greater than 10% of the test species' lifetime (e.g., Stevens and Mylecriane, 1994).

Moreover, Barton and Clewell (2000) states clearly that no uncertainty factor is needed to account for subchronic to chronic exposure. The authors report:

> Selection of changes in liver weight/body weight as a potential critical endpoint was based on its role as an early event in the toxicity process and a sensitive indicator of potential liver effects observed at later times. Therefore, based upon the mode-of-action argument that this early event is an indicator of toxicities that develop later, no adjustments for the duration of exposure would be needed, regardless of the study duration.

Finally, in 1998, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use indicated that little difference was seen in toxicity in rodents dosed for 6 months rather than one year and advocated that 6-month dosing studies in rodents be specified as chronic (ICH, 1998). European Union countries have adopted

this policy. Thus, the Tucker et al. (1982) study should be considered chronic and not subject to an uncertainty factor for adjustment from subchronic to chronic dosing.

*LOAEL to NOAEL*

EPA (2001d) applied an uncertainty factor of 3 to correct for potential differences in dose required to adjust the LOAEL to a NOAEL. However, in one of the three liver studies used (Tucker et al., 1982), the endpoint was in fact a NOAEL. In another (Berman et al., 1995), an LED10 was calculated. This metric is frequently used in a fashion similar to a NOAEL i.e., an uncertainty factor for LOAEL to NOAEL is infrequently applied to the LED10 (Faustman, 1996). In fact, the Reference Dose Technical Panel (EPA, 2001e) asserts that the LOAEL-NOAEL uncertainty factor is "unnecessary when using dose-response modeling to derive a benchmark dose, as the value at a given level of response can be derived from the dose-response model."

Finally, the endpoint of the critical studies subject to this uncertainty factor was change in the liver weight to bodyweight ratio. In all cases, the change in liver weight was not accompanied by histopathological or chemical indications of injury. It is disturbing that EPA treats these data as if they were clearly indicative of an adverse effect. Barton and Clewell (2000) clearly describe their interpretation of the nature of the liver effects as a justification for applying no LOAEL to NOAEL uncertainty factor.

*Animal to Human*

EPA (2001d) applied an uncertainty factor of 3 to account for animal to human extrapolation. This factor covers animal to human pharmacodynamic variation (i.e., species sensitivity).

Barton and Clewell (2000) state that "information on the mode of action does not support the default assumption that humans are more sensitive than animals for liver effects." Liver effects associated with TCE exposure likely involve the peroxisome proliferator-activated receptor (PPAR). Available data indicate that mice have a fully active PPAR, whereas rats and humans are less responsive (Barton and Clewell, 2000). This suggests that humans are not more sensitive than the most sensitive rodent. Indeed, Barton and Clewell (2000) report "these data indicate that the value of the uncertainty factor for interspecies extrapolation should be no greater than 1 and potentially less." The Reference Dose Technical Panel (EPA, 2001e) reports that an uncertainty factor of 3 accounts for pharmacodynamic differences, but this default factor should be adjusted when "data support the conclusion that the test species is more or equally as sensitive to the pollutant as humans."

*"Modifying Factor" for Background Exposures*

EPA (2001d) used a so-called "modifying factor" of 3 to reflect background exposures to TCE and TCE's metabolites and thereby protected against cumulative risk. EPA's use of a modifying factor for this purpose is unprecedented. The issue of cumulative risk is a risk management rather than a risk assessment issue (NRC, 1983).[14]

[14] Note also that the need to assess background sources of TCE is unclear. Wu and Schaum (2000) indicated that

Finally, note that the use of modifying factors for any purpose is disfavored. The Reference Dose Technical Panel (EPA, 2001e) considers "the modifying factor (MF) to be sufficiently subsumed in the general database uncertainty factors." Furthermore, the Panel considers "the availability of a factor that may be evoked with quantitative consequences based solely on professional judgment or assessment as being counter to the other stated intentions of risk characterization, i.e., that decisions and procedures within assessments reflect clarity, transparency, consistency and reasonableness." The Panel therefore recommended discontinuing the use of modifying factors.

* * *

Based on review of the various uncertainty factors, EPA's uncertainty factor for human variation should be reduced by at least a factor of 2 and the modifying factor should be eliminated. There also appears to be little justification for EPA's uncertainty factors for animal-to-human extrapolation, LOAEL-to-NOAEL extrapolation, and subchronic-to-chronic adjustment. Thus, EPA's overall uncertainty factor is at least an order of magnitude and more likely two orders of magnitude greater than scientifically reasonable. This recommendation is strongly supported by the RfDs derived in Barton and Clewell (2000).

ambient concentrations of trichloroethylene decreased significantly between 1987 and 1994. As such, the exposure estimates provided in EPA (2001d) are likely to be incorrect for the current situation.

NTP Proposed Listing of Naphthalene as a Carcinogen

The National Toxicology Program (NTP) has proposed to list naphthalene in the Eleventh Edition of the Report on Carcinogens as "reasonably anticipated to cause cancer in humans." As discussed below, the proposed listing is based on, but ignores, NTP's own criteria for listing chemicals as possible carcinogens.

In order to be listed as "reasonably anticipated to cause cancer in humans" by NTP, a compound generally must first meet one of two criteria. Either there must be:

> limited evidence of carcinogenicity from studies in humans which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not be adequately excluded,
>
> or
>
> sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors.

If the listing is based on "sufficient evidence" in animals, another criteria must also be met: the animal data must be "in multiple species or at multiple tissue sites; by multiple routes of exposure; or to an unusual degree with regard to incidence, site, or type of tumor or age at onset." Finally, if a chemical does not have sufficient evidence of carcinogenicity in animals, NTP can list the chemical as "reasonably anticipated to cause cancer in humans" based on other considerations of structure and mechanism.

NTP listing criteria require that all conclusions be made based on scientific judgment with consideration of dose-response, metabolism, pharmacokinetics, and other relevant information. NTP specifically states: "substances for which there is evidence of carcinogenicity in laboratory animals are not considered 'reasonably anticipated to cause cancer in humans' where there are compelling data indicating that the agent acts through mechanisms which do not operate in humans."

Based on the NTP's own criteria, NTP should not list naphthalene as "reasonably anticipated to cause cancer in humans" for two reasons. First, there is no "limited evidence of carcinogenicity from studies in humans" reported in the literature. The only human studies that have been discussed by NTP are very small health status surveys of employees of an East German coal tar company "engaged in the purification of naphthalene" conducted in the early 1970s (Wolf, 1976, 1978). Although these reports have some relevance to "naphthalene workers" because naphthalene is a component of coal tar, Wolf (1978) suggested that tar fumes in combination with heat were causative factors in the development of laryngeal cancer. In addition, the study was seriously confounded in that four of the 15 workers in the study developed laryngeal cancer and all four were smokers. In addition, all of the workers were likely to have had many confounding chemical exposures, several of which were discussed by Wolf (1976). As noted in

comments prepared by AMEC[15] on the NTP proposal to list naphthalene as a carcinogen (Appendix 5), the vast literature on the health status of thousands of workers in numerous industries who were exposed to naphthalene-containing mixtures reveals no indication that naphthalene exposure was responsible for an increase in cancer rate. Moreover, even in studies involving workplace exposure to multiple chemicals, nasal tumors, the only tumor type associated with naphthalene exposure in rodents, were not elevated. Clearly, there is not "limited evidence of carcinogenicity from studies in humans" for naphthalene.

Second, under the NTP criteria there is not "sufficient evidence of carcinogenicity from studies in experimental animals" for naphthalene. The evidence of carcinogenicity is only in one species, not multiple species; the evidence is at one tissue site, not multiple sites; the evidence is from one route, not multiple routes of exposure; and the evidence does not show an unusual high incidence or suggest that site, tumor type or age at onset were in any way unusual. Moreover, there are "compelling data indicating that the [naphthalene] acts through mechanisms which do not operate in humans." Specifically, human nasal physiology is differs significantly from rodent nasal physiology. A primary site of action for toxic effects in rats is the olfactory epithelium, which comprises a significant portion of the total nasal cavity. The rat is an obligatory nose breather and must rely on olfaction for survival. The olfactory mucosa in rats is a highly developed system of cellular structures that performs complicated integration of olfaction and air humidification. Approximately 50% of the total surface area of the posterior region of the rat nasal cavity is composed of the olfactory epithelium (Gross et al., 1982; Uraih and Maronpot, 1990). Inhaled vapors need traverse only a few millimeters past the resistant respiratory epithelium to reach the sensitive olfactory tissue in rats.

By comparison, the total surface area for chemical exposure is much less in humans (by a factor of five) since human nasal turbinates are much less convoluted than in the rodent. The olfactory epithelium comprises only about 10% of the human nasal cavity and is confined to the posterior dorsal region of the nasal cavity (Frederick et al., 1994). The ciliated respiratory epithelium is the major lining of the human nasal cavity. In humans, inhaled vapors must traverse several centimeters through the ciliated respiratory epithelium before reaching the olfactory epithelium. Through mucociliary actions, the respiratory epithelium provides a protective system for the olfactory epithelium and other respiratory tissues. As a result of these differences, the efficiency of extracting chemicals from air inhaled through the nose is much less in humans than in rodents, which rely heavily on their sense of smell to locate food. The resulting dose deposited to the human olfactory epithelium, in particular, from inspired air is far less than for rodents for any given naphthalene concentration in air.[16]

It is therefore clear that the mechanism of action in the rat is not relevant to the human, and this fact alone should require NTP to conclude that naphthalene does not meet the criteria for listing. Moreover, the empirical evidence showing a lack of nasal tumorigenic response in humans is

[15] AMEC. 2003. Comments on Proposal to List Naphthalene in the Report on Carcinogens, Eleventh Edition. Submitted to the National Toxicology Program. March 21.

[16] While the paragraphs above focus on physiological differences relevant to understanding the differences between rat and human upper respiratory tract mechanisms of actions, it is also important to note that recent NIH-funded research demonstrates that the metabolism of naphthalene differs between rodents and humans. See, e.g., Buckpitt et al.. (2002).

entirely consistent with the lack of relevance of the mechanism of action of high dose naphthalene exposure in rats to the human situation. Thus, there are "compelling data indicating that the agent acts through mechanisms which do not operate in humans."

EPA's New RfC for Naphthalene

EPA has adopted an IRIS Reference Concentration (RfC) for naphthalene 0.003 mg/m$^3$. This value is slightly lower than the ambient background concentration for naphthalene (0.0052 mg/m$^3$) in the United States (ATSDR, 1995). EPA's RfC for naphthalene therefore suggests that a substantial portion of the United States population faces health risks from exposure to naphthalene. In fact, as discussed below, there is almost certain no risk whatsoever from exposure to ambient levels of naphthalene. Not even workers exposed to occupational levels thousand of times higher than EPA's RfC are at significant risk.

EPA's RfC for naphthalene is based on nasal irritation in mice which was seen at a LOAEL of 50 mg/m$^3$. EPA derived its RfC by applying an uncertainty factor of 3000 to a human equivalent LOAEL of 9.3 mg/m$^3$. The total uncertainty factor of 3000 is comprised of factors of 10 to extrapolate from mice to humans, 10 to protect sensitive humans, 10 to extrapolate from a LOAEL to a NOAEL, and 3 for database deficiencies (IRIS, 2003).

As discussed in the previous section of these comments, using nasal effects in rodents to assess the risks of human exposure to naphthalene is inappropriate because humans are less sensitive to inhaled naphthalene than mice. Even more important, there is no need to rely on animal data to develop a naphthalene RfC for humans because several worker studies exist that can be used to determine a safe inhalation exposure level for humans (ACGIH, 1993; OSHA, 1995).

In fact, OSHA has relied on these studies to determine a time-weighted average threshold limit value (TWA-TLV) or permissible exposure level (PEL) of 50 mg/m$^3$ (10 ppm). This limit protects workers from significant risks of eye irritation and other ocular effects from exposure to naphthalene. Note that this value is five times higher than EPA's starting point for deriving the RfC (the human equivalent LOAEL of 9.3 mg/m$^3$ from the mouse study) and over 16,000 times higher than EPA's RfC.

Hoboken, New Jersey, Industrial Building Remediation

When it came to EPA's attention that an industrial building in Hoboken, New Jersey, had been illegally converted to residential use, the building was vacated and EPA sought to remediate the building under Superfund. Although it was generally agreed that the building should not be used for residential purposes after remediation, the owner proposed to continue to use it as a factory after remediation. EPA ultimately adopted a mercury remedial objective that was so stringent that it effectively required demolition of the building rather than re-use for industrial purposes.

The EPA remedial objective -- 0.44 μg of mercury per cubic meter of air – was unduly stringent because:

- EPA ignored the fact that no other organizations charged with worker protection have adopted an airborne mercury standard that is anywhere as stringent as EPA's objective. Table 2 demonstrates this.

**Table 2: National and International Occupational Standards for Elemental Mercury**

| *Standards Organization* | *Mercury Air Standard[17] ($\mu g/m^3$)* |
|---|---|
| ACGIH (US) | 25 (skin)[18] |
| NIOSH (US) | 50 (skin) |
| OSHA (US) | 100 (skin)[19] |
| Australia | 50 (skin) |
| Belgium | 100 (skin) |
| Canada | 50 |
| China | 20 |
| Egypt | 50 |
| Finland | 50 |
| France | 50 (skin) |
| Germany | 100 (skin) |
| Hungary | 20[20] |
| India | 50 |

[17] 8-hour Time-Weighted Average ("TWA").

[18] "Skin" notation indicates that standard is intended to protect against both inhalation and dermal absorption of mercury.

[19] A revised standard of 50 $\mu g/m^3$ was struck down in AFL-CIO v. OSHA, 965 F.2d 962 (11th Cir. 1992) on procedural grounds.

[20] "Target" value.

| | |
|---|---|
| Mexico | 50 |
| Poland | 50 |
| Sweden | 50 (skin) |
| Switzerland | 50 (skin) |
| Turkey | 100 (skin) |
| United Kingdom | 25 |
| World Health Organization | 25 |

- EPA's standard was derived by starting with the air concentration generally believed to be protective (25 $\mu g/m^3$) and, in effect, applying a total safety factor of over 50 to reach its objective of 0.44 $\mu g/m^3$. Although stated to be intended to protect workers from airborne exposure to mercury, the objective was in fact derived using residential exposure assumptions (exposure 24 hours a day, seven days per week).
- EPA simply ignored the evidence that the 25 $\mu g/m^3$ standard is protective for workplace exposure. Specifically:
    - The most reliable worker exposure studies (Fawer et al.., 1983; Piikivi et al.., 1989a,b,c) concluded that an occupational limit of 25 $\mu g/m^3$ is adequately protective.
    - Twenty-one studies have found that adverse effects in humans occur only at mercury exposure levels resulting in urinary concentrations above 50 µg mercury per gram of creatinine. This concentration per gram of creatinine corresponds to 110 µg of mercury per liter of urine, which in turn corresponds to an airborne exposure level of about 41 $\mu g/m^3$.

PCB TSCA "Megarule"

In June 1998, despite its own conclusion that the appropriate CSF for PCBs was in the range of 0.1 to 2.0 $(mg/kg/day)^{-1}$ (EPA, 1996a), EPA promulgated the so-called "PCB Megarule" based on a 4.0 $(mg/kg/day)^{-1}$ CSF. EPA doubled the 2.0 CSF to take into account what it conceded were unquantified "non-cancer" effects of PCBs:

> The cancer slope factor used in the risk estimates generated in this report is 4.0 $(mg/kg/day)^{-1}$. This is the value used by USEPA's Office of Toxic Substances to evaluate risks for USEPA's PCB Spill Cleanup Policy and was also requested for use here by USEPA's Office of Pollution Prevention and Toxics (OPPT) (personal communication between John Smith, USEPA and Linda Phillips, Versar, Inc., August 21, 1997) as a conservative value that would account for uncertainty associated with the presence of potentially toxic dioxin-like congeners and other uncertainties associated with the exposure/risk assumptions. This value is somewhat more conservative than the values listed in recent Agency guidance (USEPA, 1996a) and used in some of the risk assessments generated by other agencies.

USEPA, Assessment of Risks Associated with the PCB Disposal Amendments (Versar, May 11, 1998). In response to comments asking EPA to base the Megarule on the latest scientific information, EPA stated in the preamble to the final rule:

> In adopting this policy position, EPA weighed the potential benefits and costs associated with revising the final rule to reflect the most recent PCB cancer potency information. Such a change at this time would delay the issuance of the final rule and its anticipated large cost savings, for likely only very marginal benefits.

63 Fed. Reg. 35383, 35386 (June 29, 1998). EPA's "Response to Comments" background document stated:

> While the 4.0 $(mg/kg/day)^{-1}$ slope factor does not correspond with any of the cancer slope factors in the September 1996 report [the Reassessment], it does allow for additional protection from as yet unquantified risks from non-cancer human health effects and effects to the environment.

USEPA, Response to Comments Document on the Proposed Rule -- Disposal of Polychlorinated Biphenyls (May 1998) at 132.

Industry challenged the Megarule, arguing that the 4.0 $(mg/kg/day)^{-1}$ CSF could not be defended based on the record or science. Industry pointed out that it is well-known -- and accepted by

EPA and all other entities to assess risk from chemical exposure -- that cancer and non-cancer risks are not summed in the course of risk assessment. Rather, cancer and non-cancer risks are estimated separately and the more stringent of the risk estimates controls.

After lengthy settlement negotiations, EPA agreed to a remand of the 4.0 $(mg/kg/day)^{-1}$ CSF. The Court then remanded the matter to EPA. Central & Southwest Services, Inc. v. EPA, 220 F.3d 683 (5th Cir. 2000). To date, EPA has not proposed corrected Megarule standards for PCBs.

Gas Turbine Association Petition to "Delist" Gas Turbies from MACT

As discussed above, the Gas Turbine Association has petitioned EPA to "delist" gas turbines from MACT requirements pursuant to Section 112(c)(9) of the Clean Air Act on the grounds that gas turbine emissions present less than a $10^{-6}$ risk of cancer and an insignificant non-cancer risk. As previously related, USEPA is demanding that GTA use very conservative exposure assessment parameters in the risk assessment supporting the delisting petition. In addition, EPA is requiring use of a scientifically unsupportable approach to toxicity assessment

EPA is insisting that GTA's risk assessment assume that the risk from all of the carcinogenic HAPs is additive. This is inconsistent with the accepted risk assessment practice that assumes risk to be additive only when the chemicals at issue affect the same target organ or have the same mechanism of action. EPA (1986) cautions that "if the compounds in a mixture do not have the same mode of toxicologic action, dose additivity is not the most biologically plausible approach, and can lead to substantial errors in risk estimates if synergistic or antagonistic interactions occur (emphasis added)." Other agencies express similar concerns. The Scientific Committee on Food (SCF, 2002) in its research on food toxins cautioned that dose additivity requires a common mechanism of action. In addition, the Department of Energy (DOE, 1995) in its Reference Manual for CERCLA's Baseline Risk Assessment advises that "if two or more components each act by different toxicological mechanisms, additivity of risks for a common endpoint is not necessarily to be expected."

EPA understands well that it would not be appropriate to assume additivity without substantial evidence. The Food Quality Protection Act (FQPA) requires the assessment of cumulative risks that might result from exposure to pesticides and other substances that are toxic by a common mechanism. In compliance with the FQPA, EPA has set forth specific guidelines for identifying those substances that have a common mechanism of toxicity (EPA, 1999e). Those guidelines include a thorough identification and analysis of all information that can be used as the basis for determining the mechanisms of toxicity for each pesticide and a weight-of-evidence approach to support the common mechanisms of toxicity. EPA (1999e) states that "no single piece of information will suffice to support the characterization of a specific or common mechanism of toxicity; this finding will be supported by the analysis and inter-relationships of available pieces of information." In developing its guidelines, EPA (1999e) has been careful not to confuse "mechanisms of toxicity" with "site of toxic action" or "site of toxic effect." EPA's guidelines for assessing potential joint toxic actions first call for a preliminary grouping of those chemicals that might cause a common toxic effect by a common mechanism. Criteria used to preliminarily group chemicals include: structural similarity; general mechanism of mammalian toxicity; and a particular toxic effect (EPA, 1999e). EPA (1999e) emphasizes that chemicals identified under this first step "will not be included in a cumulative risk assessment if it is determined that they do not cause a common toxic effect by a common mechanism." In step 2, EPA (1999e) definitively identifies those chemicals that cause a common toxic effect and, in step 3, determines the mechanism by which each chemical causes that effect. In the remaining steps, EPA (1999e) compares each mechanism to identify those chemicals with both a common toxic effect and a common mechanism. By following this multiple-step approach that involves a thorough

evaluation of toxicity data, EPA will determine that many chemicals identified in the preliminary step will not be carried forward.

Finally, it must be noted that the arithmetic summing of cancer risk is incorrect for two reasons. First, it is not appropriate to sum cancer risks of chemicals with different cancer classifications because the human cancer risk of those chemicals which are less likely to be human carcinogens will be overstated. As explained by DOE (1995), the addition of slope factors for multiple chemicals in a mixture sums all carcinogens equally, regardless of their carcinogenicity classification. Adding cancer risk is also mathematically incorrect. Cancer risks are typically based on cancer slope factors that represent the upper 95th percentile estimates of potency. These 95th percentile estimates are not strictly additive (EPA, 1989; Lang, 1995). Burmaster and Lehr (1991) show that when three 95th percentile values are combined, the outcome represents the 99.99th percentile. EPA (1989) agrees, noting that "when adding cancer slope factors from multiple chemicals, the total cancer risk estimate might become more conservative."

EPA has also asked that GTA's risk assessment apply the additivity approach to non-carcinogens. However, the Agency has cautioned against this approach:

> Application of the hazard index equation to a number of compounds that are not expected to induce the same type of effects or that do not act by the same mechanism, although appropriate as a screening-level approach, could overestimate the potential for effects. This possibility is generally not of concern if only one or two substances are responsible for driving the HI above unity. If the HI is greater than unity as a consequence of summing several hazard quotients of similar value, it would be appropriate to segregate the compounds by effect and by mechanism of action and to derive separate hazard indices for each group.

EPA (1989)

Use of the "Toxicity Equivalency Quotient" Approach

In the draft dioxin reassessment, EPA has proposed to use the Toxicity Equivalency Quotient (TEQ) approach to assess the toxicity of PCBs. As discussed in detail in Appendix 3, the TEQ approach, as applied to PCB congeners, is based largely on assumptions that are of questionable scientific validity and are inconsistent with existing experimental data. The result is to inappropriately and substantially overpredict both the cancer and non-cancer toxicity of PCBs.

The TEQ approach is based on the finding that certain chemicals, including 12 coplanar PCB congeners, exhibit structural and toxicokinetic similarities to TCDD. These chemicals are said to act through the same mechanism as TCDD and related compounds, namely binding with the aryl hydrocarbon receptor (AhR). Other chemicals that bind with the AhR include polynuclear aromatic hydrocarbons, certain hormones, certain drugs, and a chemical formed by the human metabolism of the indole glucobrassicin (which is found in cruciferous vegetables, including cabbage, cauliflower, and broccoli) (Fiala et al., 1985; Hodgson and Levi, 1987). The flaws of the TEQ approach, as applied to PCB congeners, can be summarized as follows:

- The TEF approach is inappropriate for assessing PCB toxicity because it is based on the unproven assumption that PCBs have additive toxic effects. The fact that a chemical binds with the AhR does not mean that it will cause an adverse effect. In fact, chemicals that bind with the AhR can have a beneficial effect (e.g., triggering a normal physiological response like enzyme induction), an adverse effect, or no effect.
- A significant amount of laboratory data indicates that TEFs are not, in fact, additive. Moreover, the TEQ approach ignores the long-established approach that evaluates PCB toxicity using cancer slope factors (CSFs) for PCB mixtures. If the TEQ methodology for PCBs is correct, then it should accurately predict the toxicity of PCB mixtures. Appendix 3 demonstrates that the TEQ approach overpredicts the carcinogenicity of PCB mixtures by over an order of magnitude.
- Appendix 3 also explains how laboratory evidence demonstrates that the TEQ approach over-predicts the noncancer toxicity of PCBs. For example, Bannister et al. (1987) treated mice with TCDD alone and with a mixture of TCDD and between 1,300 and 20,000 times as much Aroclor 1254. The mice treated with TCDD alone showed a large depression in the formation of certain infection fighting cells. The mice treated with the TCDD/Aroclor 1254 mixture showed no depression. Apparently, the Aroclor 1254, which contains agonists, partial agonists and antagonists, overall had an antagonist effect that wholly offset the agonist effect of the TCDD.

  EPA's advocacy of the unproven TEQ approach is a good example of Agency action that is not based on sound science and, moreover, is demonstrably poor at accurately estimating toxicity. It should be an high priority for EPA to reject scientific approaches that do not comport with the evidence.

## II. Ecological Risk Examples

### A. Toxicity Assessment

Ecological risk assessments are performed by comparing exposure to Toxicity Reference Values (TRVs), which are analogous to the RfDs used in human health risk assessments. There is currently no standard approach for assessing potential carcinogenic effects in ERAs. Recent guidance, the Ecological Soil Screening Level Guidance or EcoSSL (EPA, 2003b), summarizes four methods to derive TRVs: (1) critical study approach; (2) benchmark dose model approach; (3) distribution approach; and (4) weight-of-evidence approach. These are summarized below:

- The critical study approach has been the most common method used to derive TRVs (e.g., Sample et al., 1996). Similar to the derivation of a human health RfD, uncertainty factors are applied to a LOAEL or NOAEL from the critical study. The selection of the appropriate critical study and uncertainty factor(s) are key to the determination of whether the derived TRV is overly conservative or appropriate for the particular site.
- The benchmark dose approach is also based on a critical study, but uses the benchmark dose model (EPA, 2000), in lieu of NOAELs or LOAELs, to derive the TRV. This approach does not require uncertainty factors, but instead uses the entire dose-response relationship from the critical study and fits an appropriate curve to these values. The TRV is then assigned as the value that represents an incremental effect of 10% at the 95% confidence level. The selection of the appropriate critical study is key to the determination of whether the TRV is overly conservative or appropriate for the particular site. Although not commonly employed by USEPA for TRV development, the BMD approach has been used by other government entities (e.g., USACHPPM, 2000).
- The distribution approach uses probability density function that represents the sensitivity of different species to the evaluated endpoint at a particular level (such as the LD50). Although this approach has the potential to address the slopes of the dose-response curves, it suffers from the lack of an adequate toxicological database to best define the probability density function.
- The weight-of-evidence approach combines the results from a number of studies using different measurement endpoints (e.g., growth, reproduction) and test organisms. The TRV is calculated as the geometric mean of the NOAELs for growth and reproduction effects, since these are most relevant to potential population effects.

EPA Recommended "Weight-of-Evidence" Approach to Derive TRVs

Although the EcoSSL Guidance discusses the four approaches to derive TRVs (EPA, 2003b), the Agency chose to select the weight-of-evidence approach to calculate SSLs because the weight-of-evidence approach considers:

> all of the extracted toxicological data in place of the selection of one critical study. The use of the critical study approach would require considerable professional judgment thereby decreasing the transparency and reproducibility of the wildlife TRV derivation process. To avoid foreseen conflicts over selection of "one" result; to prevent the need for "committee" selection and to attain transparency and reproducibility this method [critical study approach] was not selected.

Although the weight-of-evidence approach may be appropriate for deriving screening level values, it should not be used for site-specific ecological risk assessments because the weight-of-evidence approach does not address the measurement endpoints that may be relevant to key ecological receptors of interest for a particular site. For example, when evaluating the studies considered for the weight-of-evidence assessment, less weight should be given to studies that evaluate the toxicity of the given chemical to receptors that are not found at the particular site, to studies of chemicals whose form may not be relevant to the site-specific form (e.g., use of lead salts when lead may be bound to sulfides in the environment), and to studies whose designs are inconsistent with the exposure that may occur under the environmental conditions at issue (e.g., plant toxicity studies based on hydroponic exposure to the salt form of the metal). EPA (2003b) did not compare the weight-of-evidence approach to the more commonly applied critical study approach, or to the other two methods (the benchmark dose or distribution approaches), implying that the weight-of-evidence approach may not have received adequate peer review. EPA has not demonstrated that the weight-of-evidence approach will result in TRV values that are appropriate for EcoSSL development, much less for evaluation of site-specific conditions.

The goal of the EcoSSl development process is to provide levels that can be used to screen chemicals on a site-specific basis. The TRVs developed for EcoSSLs are based on no effect levels and do not represent values suitable for the protection of populations that have been suggested as assessment endpoints. Exceedance of the TRV does not necessarily imply that there will be an effect, much less an adverse effect. Thus, the use of these TRVs will result in EcoSSLs that will be so low as to not exclude (screen out) any compounds.

EPA Avian TRV for Dioxin for the Hudson River

USEPA has inconsistently applied uncertainty factors for deriving the TRV for dioxins in avian species based on the Nosek et al. (1992) study, which involved a 10-week exposure period. Oak Ridge National Lab's assessment of this study concluded that effects on survival, egg production, and egg hatchability were observed only at the maximum dose (Sample et al., 1996). Because this study considered exposure throughout a critical life stage (reproduction), the upper no effect dose level (0.1 µg/kg-week) was considered to be a chronic NOAEL. Therefore, an uncertainty factor was not applied, or required, to derive the TRV, which was calculated at 1.4 x $10^{-5}$ mg/kg-day. USEPA's Screening Level Ecological Risk Assessment Protocol for Combustion Facilities, simply rounded the TRV to 1 x 10-5 mg/kg-day, but used the same approach (EPA, 1999f). USEPA's Data Collection for the Hazardous Waste Identification Rule, (Section 14: Ecological Benchmarks) took a slightly different approach, assigning the TRV as the geometric mean of the NOAEL and LOAEL from the same study (4.4 x $10^{-5}$ mg/kg-day), but did not apply an uncertainty factor (EPA, 1999g). Despite the precedent established by its own documents, EPA (2000b), in its ecological assessment of the Upper Hudson River, used a TRV of 1.4 x $10^{-6}$ mg/kg-day for the evaluation of dioxin-like PCB congeners. EPA (2000b) assumed that the 10-week exposure period represented a subchronic rather than chronic exposure and applied an uncertainty factor of 10 to account for this, resulting in a 10-fold more conservative TRV than used elsewhere.

EPA Otter TRV for PCBs for the Hudson River

The Upper Hudson River Revised Baseline Ecological Risk Assessment (RBERA) developed conservative TRVs. The RBERA did not report any species-specific studies for the development of the TRVs for River otters. Instead, the NOAEL (0.004 mg/kg-day) and LOAEL (0.04 mg/kg-day) identified for mink were used for the phylogentically similar River otter (both are members of the Family Mustelidae). The study used to develop the TRVs for the mink (Restum et al., 1998) included confounding exposures to pesticides. The authors did not attempt to segregate the potential contribution of the pesticides to the evaluated endpoint (kit survival), nor was this uncertainty included in the TRV development. The derivation of appropriate TRVs is critical not only in the RBERA, but also in the assessment of remedial measures. For example, when the TRVs for mink and River otter were adjusted to reflect appropriate interspecies relationships and realistic exposures (e.g., area use factors), the source control alternative achieves lower risks to mink and otter than dredging in 34 of the 40 miles of the Upper Hudson River.

B. Risk Characterization

Risk characterization in an ERA includes several components (EPA, 1997a): (1) the integration of exposure profiles with exposure-effects information; (2) calculation of hazard quotients (HQs) or hazard indices (HIs); (3) discussion of approaches to interpret the risk results; (4) identification of a threshold for adverse effects on the assessment endpoints; and (5) summary of the associated uncertainties. The most common metrics for ecological risks are the HQ and HI. An HQ less than one (unity) indicates that the contaminant alone is unlikely to cause adverse ecological effects. Similarly, when the HI (the sum of HQs for chemicals with similar mechanisms of toxicity and assessment endpoints) is less than one, the group of chemicals is unlikely to result in adverse ecological effects.

Risks are then combined across exposure pathways for the representative receptor(s) to develop receptor group-specific risks/hazards. The focus is typically on water ingestion and dietary exposure routes, although this can be species-specific (e.g., dermal transport through feet in wading birds; inhalation of volatiles by burrowing animals). The uncertainty in the risk estimate is then assessed. Although uncertainty assessment is typically qualitative, quantitative approaches are preferable, especially if probabilistic methods are used as part of the uncertainty assessment.

EPA does not provide any formal guidance on the determination of a "level of significance" when the HQ or HI is above one. EPA (1997a) does recommend that:

> The lower bound of the threshold would be based on consistent conservative assumptions and NOAEL toxicity values. The upper bound would be based on observed impacts or predictions that ecological impacts could occur. This upper bound would be developed using consistent assumptions, site-specific data, LOAEL toxicity values, or an impact evaluation.

Notwithstanding this guidance, the use of a bounding approach is rarely seen in ERAs.

One approach to assess the significance of an exceedance of the HI or HQ is in the context of potential population-level effects. EPA (1997a) recommends that potential ecological risks should be assessed at the population-level for all but threatened and endangered species. Although no explicit guidance is provided, this is typically accomplished through the use of measurement endpoints that are related to population effects (e.g., using TRVs based on growth or reproductive effects).

## Fox River ERA

The Fox River/Green Bay ROD relied, in part, on an ERA to justify selection of a dredging remedy. However, the ERA is seriously defective and inconsistent with USEPA guidance. In fact, the ERA is little more than a screening level assessment which, under EPA guidance, may not be used as the basis of a remedy decision.

Under EPA guidance (EPA, 1997a), an ERA is to be performed as a stepwise process. This process moves from a conservative screening analysis to definitive "baseline" risk characterization, with the latter employing site-specific data as much as possible. In short, screening level risk assessments are conducted to support a fundamental threshold decision: Does a site require additional risk assessment? Screening level assessments are not conducted to support major risk management decisions.

The Fox River ERA is inconsistent with this guidance. Although the ERA discusses the substantial site-specific data base which was compiled by the Fox River PRPs, the US Fish and Wildlife Service, USEPA, WDNR, universities, and other organizations and institutions, the ERA utterly fails to use this information in the risk assessment. Instead, the ERA is based on conservative assumptions and generic exposure scenarios, and demonstrably overstates ecological risk posed by the presence of PCBs in the Fox River. A few examples of the ERA's deficiencies follow:

- The ERA is highly misleading in its treatment of site-specific habitat data. In response to industry comments, the ERA summarizes habitat information for a number of ecological receptors and cites a detailed habitat analyses conducted by the Fox River PRPs. However, the ERA then proceeds to include the site-specific habitat information only in qualitative discussions in an introductory section of the ERA. The site-specific habitat information is not used for the purpose of risk quantification. The ERA offers no explanation for this omission.
- Ignoring site-specific habitat information leads the ERA to false conclusions. For example, the ERA's highest hazard quotient projections for mink are in one reach of the Fox River and in one area of Green Bay. However, data cited by the ERA clearly show that there are very few mink in these areas. Thus there is, in fact, little or no risk to mink populations.
- The ERA erroneously assumes that risk derives equally from PCBs distributed in all areas of the river. Thus, the ERA calculates a single sediment quality threshold to be applied to all sediments whether or not they contribute substantially to fish exposure. If the ERA had accurately accounted for fish habitat preferences, it would have been clear that a single reach-wide sediment quality threshold is inappropriate and not scientifically supported.

By ignoring readily available site-specific information, the ERA provided inaccurate risk characterization, an ineffective foundation for risk management decisionmaking, and a risk assessment that is not in keeping with the provisions of applicable USEPA guidance.

## Upper Hudson River ERA

The Upper Hudson River Revised Baseline Ecological Risk Assessment (RBERA) was considered in making the remedial decision for the Upper Hudson River in New York. Under EPA's own guidance (EPA, 1997a), however, the results of the RBERA should not have been used to determine remedial action, because the approach actually employed by EPA's contractor was designed for screening-level applications. This RBERA is based principally on conservative data and assumptions that are deliberately designed to be conservative to minimize the possibility that any potential adverse effects will be missed in a screening-level analysis. As such, these data and assumptions overstate the actual effects of most chemicals at most sites. For the baseline ecological risk assessment of so prominent a site as the Upper Hudson River, EPA should have refined its toxicity quotient-based approach to incorporate more site-specific information. In addition, EPA should have used an approach that incorporates data on the actual conditions of fish and wildlife populations in and along the Hudson River. In fact, EPA (2000d) discussed several field studies in the RBERA, but dismissed their relevance and did not integrate the results into the ecological risk assessment.

On behalf of EPA, Eastern Research Group coordinated a review of the Upper Hudson River ecological risk assessment by seven independent peer reviewers. This peer review group sharply criticized EPA's work product, concluding that EPA's draft ecological risk assessment represented a screening-level effort. The peer reviewers provided EPA with specific recommendations to reduce the conservatism and recommended that more sophisticated approaches be used for evaluating ecological risks. For the most part, EPA either failed to implement these recommendations, implemented the recommendations incorrectly, or made offsetting changes to the recommendations that resulted in little reduction to the level of conservatism.

For example, the peer reviewers found that EPA did not embrace an appropriate weight-of evidence approach in conducting the risk assessment. The peer reviewers "questioned why EPA's conceptual site model artificially constrains the risk assessment to the main channel of the Upper Hudson River, given the fact that many receptors (e.g., birds, mammals, and fish) may use a far broader range of habitat," and "reviewers were concerned that the risk assessment, with its current spatial construct, becomes too narrow in scope" (U.S. EPA 2000d, p. 2-10). In conclusion, the peer review group unanimously agreed that EPA's characterization of the ecological setting was inadequate: Without a description of the habitats, the species occupying the Upper Hudson River, and the spatial and temporal use of habitats by species considered in the conceptual site model, the reviewers did not think it was possible to defend the risk characterization" (U.S. EPA 2000d, p. 2-2).

PCB Worm Tissue Criterion for the Historic Area Remediation Site

In October 2002, EPA developed Proposed Polychlorinated Biphenyl Worm Tissue Criterion for the Historic Area Remediation Site (HARS) (67 FR 62659). This document established a HARS-specific worm tissue PCB criterion of 113 parts per billion (ppb) for use in determining the suitability of proposed dredged material for use as remediation material. The 113 ppb criterion is based on a number of conservative assumptions including the following: (1) 100% of fish consumed by New Jersey anglers are sport-caught saltwater finfish, even though the data allow one to distinguish between salt and fresh water fishing; (2) 100% of the fish consumed are caught at the HARS; (3) all species consumed by recreational anglers are available at the HARS; (4) anglers fish consistently every year for 70 years; (5) there is no loss of contaminants due to cooking methods; (6) the site use factor of 77.7% for all fish species is not supported by commercial landings in the vicinity of HARS; and (7) use of a trophic transfer factor of 3 for all organics does not properly capture their potential for bioaccumulation. The final rule was issued on March 17, 2003 (68 FR 12592). The criterion remained 113 ppb with no adjustment to the conservative assumptions.

Tier II Great Lakes Initiative Water Quality Criteria

In the Great Lakes Water Quality Initiative (GLWQI), EPA proposed a two-tiered approach to deriving water quality criteria. A Tier I water quality criterion is derived when specific data requirements are met (e.g., sufficient toxicological data exist for eight taxonomic groups). These data requirements are identical to those that EPA has used historically as the minimum requirements for calculation of ambient water quality criteria. Under the GLWQI regulations, a Tier II water quality value can be derived if the data required to derive a Tier I value are not available, or if the data are not of high quality.

Because Tier II criteria are to be derived based on incomplete or inferior data, EPA builds in several levels of conservatism in the calculations. However, as discussed below, it is easily seen that using the EPA's Tier II derivation process often yields grossly over-conservative water quality criteria.

The approach used to derive acute and chronic Tier II values is as follows[21]:

- The available toxicity test results are ordered by genus and the geometric mean of the test results is calculated for each genus. The genus mean values are ranked from lowest to highest and counted.
- The lowest genus mean value is divided by the secondary acute factor (SAF), which is effectively a safety factor. The SAF ranges from 21.9 to 4.3 and decreases as the number of suitable studies available increases. That is, the more data available, the smaller the safety factor. The resulting number is called a secondary acute value (SAV).
- The Tier II acute value is the SAV divided by two.
- The secondary acute-to-chronic ratio (SACR) is the geometric mean of the ratios of acute and chronic toxic concentrations from at least three studies that have investigated both effects. If less than three studies are available, the missing values are replaced with a default value of eighteen.
- The Tier II chronic value is the SAV divided by the SACR.

The approach used to derive Tier II values can result in extremely low values, particularly when only a few acceptable toxicity studies are available (Alsop and Unwin, 1994). This is because the amount of conservatism in the Tier II value increases as the number of suitable studies decreases. For example, the comparison of chronic Tier I values for nine metals to their corresponding Tier II values show that the Tier II values overestimate the Tier I values from 3 to 16,000 times at the 95th percentile of the secondary acute factor (Alsop and Unwin, 1994). As another example, Suter and Tsao (1996) used the Tier II approach to develop potential screening benchmarks for protection of aquatic life from common contaminants in water. Because the Tier II values for sodium chloride were below commonly occurring ambient concentrations of this

[21] The example presented assumes that toxicity data for a daphnid are available. If no toxicity data for a daphnid are available, Tier II values cannot be developed.

salt, they were judged to be inappropriate by the study authors and were not presented (Suter and Tsao, 1996).

* * *

III. References

ACGIH. 1993. Threshold limit values (TLVs) for chemical substances in the work environment for 1993-1994. American Conference of Government Industrial Hygienists. Cincinnati, OH.

Alsop, W.R. and J.Unwin. 1994. Tier II Values for the Protection of Freshwater Aquatic Life. Proceedings of the 1994 TAPPI Conference. Portland, Oregon.

AMEC Earth & Environmental. 2002. Development of a Revised Chronic Reference Dose for Polychlorinated Biphenyls (Aroclor 1254) Based on Empirical Data.

AMEC Earth & Environmental. 2002a. Alternative Human Health Risk Assessment of the Lower Fox River and Green Bay, Wisconsin. January 18.

American Industrial Health Council 1999. Letter to William P. Wood, USEPA Risk Assessment Forum, on Revised EPA Guidelines for Carcinogen Risk Assessment.

Argus Research Laboratories inc (1999) Oral (drinking water) two-generation (one litter per generation) reproduction study of ammonium perchlorate in rats. Horsham, PA: Argus Research Laboratories, Inc; protocol no. 1416-001.

Argus Research Laboratories, Inc. (2001) Hormone, thyroid and neurohistological effects of oral (drinking water) exposure to ammonium perchlorate in pregnant and lactating rats and in fetuses and nursing pups exposed to ammonium perchlorate during gestation or via maternal milk. Horsham, PA: protocol no. ARGUS 1416-003

ATSDR. 1995. Toxicological Profile for Naphthalene, 1-Methylnapthalene, 2-Methylnapthalene. Update. August.

Bannister, R., D. Davis, T. Zacharewski et al. 1987. Aroclor 1254 as a 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin antagonist: Effects on enzyme induction and immunotoxicity. Toxicol. 46:29-42.

Barton, H.A. and H. J. Clewell III. 2000. Evaluating noncancer effects of trichloroethylene: Dosimetry, mode of action and risk assessment. Environmental Health Perspectives, Supplement 2 108:323-334.

Beck B.D. Connolly R.B., Dourson M.L., Guth D., Hattis D., Kimmel C. and Lewis S.C. 1992. Improvements in Quantitative Noncancer Risk Assessment Fundamental and Applied Tox. 20:1-14.

Bekkedal MYV, Carpenter T, Smith J, Ademujohn C, Maken D, Mattie DR (2000) A neurodevelopmental study of the effects of ammonium perchlorate on the motor activity of pre-weanling rat pups. Wright Patterson Air Force Base, OH; Naval Health Research Center Detachment, Neurobehavioral effects laboratory; report no. TOXDET- 00-03

Berman, E., M. Schlicht, V. Moser, R. MacPhail. 1995. A multidisciplinary approach to toxicological screening. I: Systemic toxicity. Journal of Toxicology and Environmental Health 45:127-143.

Brechner RJ, Parkhurst GD, Humble WO, Brown MB, Herman WH. 2000. Ammonium perchlorate contamination of Colorado River drinking water is associated with abnormal thyroid function in newborns in Arizona. J Occup Environ Med. 42(8):777-82

Buben, J.A. and E.J. O'Flaherty. 1985. Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: a dose-effect study. Toxicol Appl. Pharmacol. 78:105-122.

Buckpitt, A., Boland, B., Isbell, M., Morin, D. Shultz, M., Baldwin, R., Chan, K., Karlsson, A., Lin, C., Taff, A., West, J., Fanucchi, M., Van Winkle, L., and Plopper, C. 2002. Naphthalene-induced respiratory tract toxicity: Metabolic mechanisms of toxicity. Drug Metabolism Reviews. 34(4):791-820.

Burmaster, D.E. and J.H. Lehr. 1991. It's Time to Make Risk Assessment a Science. Ground Water Monitoring Review XI(3):5-15.

Calabrese, E.J., E.J. Stanek, C.E. Gilbert, and R.M. Barnes. 1990. Preliminary adult soil ingestion estimates: results of a pilot study. Regul Toxicol Pharmacol. Aug;12(1):88-95.

Calabrese, E.J., E.J. Stanek, P. Pekow, and R.M. Barnes. 1997. Soil ingestion estimates for children residing on a superfund site. Ecotoxicol Environ Saf. Apr;36(3):258-68.

ChemRisk. 1991. Consumption of Freshwater Fish from Maine Lakes and Ponds. Portland, Maine. September 6.

Cicmanec, J.L. and K.A. Poirier. 1995. Selected applications of reduced uncertainty factors in noncancer risk assessment. Hum. Ecol. Risk Assess. 1(5):637-640.

Clewell, H.J. III, P. Robinan Gentry, T.R. Covington, and J.M. Gearhart. 2000. Development of a physiologically based pharmacokinetic model of trichloroethylene and its metabolites for use in risk assessment. Environmental Health Perspectives, Supplement 2 108:283-306.

Connelly, N.A., B.A.Knuth & C.A.Bisogni. 1992. Effects of the Health Advisory Changes on Fishing Habits and Fish Consumption in New York Sport Fisheries. Human Dimension Research Unit. Cornell University (Report for the New York Sea Grant Institute Project No. R/FHD-2-PD).

Connelly, N.A., B.A. Knuth, and T.L. Brown. 1996. Sportfish Consumption Patterns of Lake Ontario Anglers and the Relationship to Health Advisories. North American Journal of Fisheries Management 16:90-101.

Crump K. 1999. Benchmark doses for perchlorate obtained from Lamm et al (1999) study of thyroid function in perchlorate workers. Comments submitted to EPA external peer review panel.

Crump C, Michaud P, Tellez R, Reyes C, Gonzalez G, Montgomery EL, Crump KS, Lobo G, Becerra C, Gibbs JP. 2000. Does perchlorate in drinking water affect thyroid function in newborns or school-age children? J Occup Environ Med. 42(6):603-12

Crump C, Weiss NS and Goodman G. 2001. Methods and conclusions of the Arizona Perchlorate Study. J Occup Environ Med. 43(4):307-9.

Crump K, Goodman G. 2003. Benchmark analysis for the perchlorate inhibition of thyroidal radioiodine uptake utilizing a model for the observed dependence of uptake and inhibition on iodine excretion. Comments submitted to Cal/EPA OEHHA

Delzell, E; N. Sathiakumar, and M. Hovinga. 1996. A follow-up study of synthetic rubber workers. Toxicology 113:182-189.

DOE. Department of Energy. 1995. CERCLA Baseline Risk Assessment Reference Manual for Toxicity & Exposure Assessment and Risk Characterization. U.S. Department of Energy, Office of Environmental Policy & Assistance RCRA/CERCLA Division. Washington, D.C. March.

Dourson, M.L. and J. Stara. 1988. Regulatory history and experimental support of uncertainty (safety) factors. Regulatory Toxicology and Pharmacology 3:224-238.

Dourson M.L., Felter S.P. and Robinson D. 1996. Evolution of Science-Based Uncertainty Factors in Noncancer Risk Assessment. Reg. Tox. and Pharmacology 24: 108-120.

Ebert, E.S., N.W. Harrington, K.J. Boyle, J.W. Knight, and R.E. Keenan. 1993. Estimating consumption of freshwater fish among Maine anglers. N. Am. J. Fish. Mgt. 13:737-745.

Ebert, E.S., S.H. Su, T.J. Barry, M.N. Gray, and N.W. Harrington. 1996. Estimated Rates of fish consumption by anglers participating in the Connecticut Housatonic River creel survey. *N.* Am. J. Fish. Mngt. 16:81-89.

EPA. 1986. Guidelines for health risk assessment of chemical mixtures. Federal Register 51(185):34014-34025.

EPA. 1986a. Guidelines for Carcinogen Risk Assessment. Federal Register 51(185):33992-34003.

EPA. 1989. Risk Assessment Guidance for Superfund; Volume I: Human Health Evaluation Manual (Part A) - Interim Final. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, D.C. EPA/540/1-89/002. December.

EPA. 1991. RAGS Volume I: Human Health Evaluation Manual, Supplemental Guidance: Standard Default Exposure Factors, OSWER Directive 9285.6-03.

EPA. 1992. Provisional Non-cancer and Cancer Toxicity Values for Potassium Perchlorate (CASRN 7778-74-7) (Aerojet General Corp./CA), Memorandum from Joan S. Dollarhide, Superfund Health Risk Technical Support Center, Environmental Criteria and Assessment Office, Office of Research and Development, to Dan Stralka, US EPA Region IX.

EPA. 1992a. Guidelines for Exposure Assessment. Federal Register 57(104): 22888-22938.

EPA. 1993. Use of IRIS Values in Superfund Risk Assessment.. OSWER Directive 9285.7-16.

EPA. 1995. Correspondence from Joan S. Dollarhide, National Center for Environmental Assessment, Office of Research and Development, to Mike Girrard, Chairman, Perchlorate Study Group.

EPA. 1995a. Land Use in the CERCLA Remedy Selection Process. OSWER Directive No. 9355.7-04. May 25.

EPA. 1995b. Risk Characterization memorandum from Administrator Carol Browner

EPA. 1996. Proposed Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency, Office of Research and Development. EPA/600/P-96/003C. April.

EPA. 1996a. PCBs: Cancer Dose Assessment and Application to Environmental Mixtures. U.S. Environmental Protection Agency, Office of Research and Development. EPA/600/P-96/001. Washington, D.C.

EPA. 1997a. Ecological Risk Assessment Guidelines for Superfund: Process for Designing and Conducting Ecological Risk Assessments, Interim Final. Office of Solid Waste and Emergency Response. EPA 540-R-97-006. June 1997.

EPA. 1997b. Exposure Factors Handbook, Volumes 1, II and III. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, D.C. EPA/600/P-95/002Fa,b,c. August.

EPA. 1997c. EPA Policy for Use of Probabilistic Analysis in Risk Assessment

EPA. 1998a. Guidelines for neurotoxicity risk assessment. Federal Register 63(93):26926-26954.

EPA. 1998b. Health risk assessment for 1,3-butadiene, external review draft. U.S. Environmental Protection Agency, Office of Research and Development. EPA/600/P-98/001A. January.

EPA. 1999. Guidance for Conducting Health Risk Assessment of Chemical Mixtures. U.S. Environmental Protection Agency. NCEA-C-0148. External Scientific Peer Review Draft. April. http://www.epa.gov/nceawww1/pdfs/mixtures.pdf

EPA. 1999a. Final Guidance: Ecological Risk Assessment and Risk Management Principles for Superfund Sites. Office of Solid Waste and Emergency Response. OSWER Directive 9285.7-28. October.

EPA. 1999b. Draft Guidelines for Carcinogen Risk Assessment. July.

EPA. 1999c. "Risk Assessment Guidance for Superfund Volume I - Human Health Evaluation Manual Supplemental Guidance Dermal Risk Assessment Interim Guidance." Office of Emergency and Remedial Response, Washington, DC. March 1999. Draft.

EPA. 1999d. Memorandum from A. Koppikar, National Center for Environmental Assessment, Office of Research and Development, to L. McKelvey, Emissions Standards Division, Office of Air Quality Plannnig and Standards. April 6.

EPA. 1999e. Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity. U.S. Environmental Protection Agency. January.

EPA, 1999f. Screening Level Ecological Risk Assessment Protocol for Hazardous Waste Combustion Facilities. OSWER. EPA530-D-99-001A. August.

EPA, 1999g. Data Collection for the Hazardous Waste Identification Rule, Section 14: Ecological Benchmarks. Draft. October.

EPA. 2000. Benchmark Dose Technical Guidance Document. EPA/630/R-00/001. October. 87p.

EPA. 2000a. Presenter's Manual for: "Superfund Risk Assessment and How You Can Help." EPA/540/R-99/013. Office of Solid Waste and Emergency Response. July 2000.

EPA. 2000b. Revised baseline ecological risk assessment, Hudson River PCBs reassessment RI/FS. U.S. Environmental Protection Agency.

EPA. 2000c. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, D.C. EPA/630/R-00/002. August.

EPA. 2000d. Report on the peer review of the ecological risk assessment for the Hudson River PCBs Superfund Site. Final report. Prepared by Eastern Research Group, Inc

EPA. 2000f. Further Site Characterization and Analysis, Revised Human Health Risk Assessment (HHRA) Volume 2F, Hudson River PCBs Reassessment RI/FS. Prepared for the USEPA Region 2 and USACE by TAMS Consultants, Inc. and Gradient Corporation.

EPA. 2001. Dioxin Reassessment – An SAB Review of the Office of Research and Development's Reassessment of Dioxin. U.S. Environmental Protection Agency, Science Advisory Board, Washington, D.C. EPA-SAB-EC-01-006. May.

EPA. 2001a. Risk Assessment Guidance for Superfund: Volume 3 - (Part A, Process for Conducting Probabilistic Risk Assessment). Final. United States Environmental Protection Agency, Solid Waste and Emergency Response. EPA 540-R-02-002. December.

EPA. 2001b. Planning for Ecological Risk Assessment: Developing Management Objectives. EPA/630/R-01/001A. June.

EPA. 2001c. Supplemental Guidance for Developing Soil Screening Levels for Superfund Sites. Peer Review Draft. OSWER 9355.4-24. March 2001.

EPA. 2001d. Trichloroethylene Health Risk Assessment: Synthesis and Characterization. Office of Research and Development, US Environmental Protection Agency. EPA/600/P-01/002A. August.

EPA. 2001e. A Review of the Reference Dose and Reference Concentration Processes. Reference Dose (RfD) Technical Panel, Risk Assessment Forum, US Environmental Protection Agency. NCEA-F-1104. August. Internal Review Draft.

EPA. 2001f. Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment) Interim Review Draft. Office of Emergency and Remedial Response. U.S. Environmental Protection Agency. Washington, DC. EPA/540/R/99/005. September.

EPA. 2002. Preliminary Remedial Goals guidance. Region 9.

EPA. 2002a. An SAB Report: A Framework for Assessing and Reporting on Ecological Condition. Science Advisory Board. EPA-SAB-EPEC-02-xxx. March. External Review Draft .

EPA. 2002b. Region 9 PRG Table 2002.
www.epa.gov/region09/waste/sfund/prg/files/02userguide.pdf

EPA. 2002c. Health assessment document for 1,3-butadiene. U.S. Environmental Protection Agency, Office of Research and Development, Washington, DC. EPA/600/P-98/001. October.

EPA. 2002d. Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization. EPA External Review Draft (Jan. 16, 2002).

EPA. 2003a. Draft Final Guidelines for Carcinogen Risk Assessment. External Review Draft. February.

EPA. 2003b. Ecological Soil Screening Levels (Eco-SSLs) Standard Operating Procedure (SOP) #4: Derivation of Wildlife Toxicity Reference Value (TRV). Attachment 4-5, Guidance for Developing Ecological Soil Screening Levels. March 2003.

Faustman, E. 1996. Review of Noncancer Risk Assessment: Application of Benchmark Dose Methods. Prepared for the Commission on Risk Assessment and Risk Management.

Fawer, R.F., U. DeRibaupierre, M.P. Guillemin, M. Berode and M. Lobe. 1983. Measurement of hand tremor induced by industrial exposure to metallic mercury. J. Ind. Med. 40: 204-208.

Fiala, E.S., B.S. Reddy, and H.H. Weisburger. 1985. Naturally occurring anticarcinogenic substances in foodstuffs. In Annual Review of Nutrition, pp. 295-321. Volume 5. Palo Alto: Annual Review Inc.

Frederick, CR; Udinsky, JR; Finch, L. 1994. The regional hydrolysis of ethyl acrylate to acrylic acid in the rat nasal cavity. Toxicol Lett 70:49-56.

Gibbs JP, Ahmad R, Crump KS, Houck DP, Leveille TS, Findley JE, Francis M. 1998. Evaluation of a population with occupational exposure to airborne ammonium perchlorate for possible acute or chronic effects on thyroid function. J Occup Environ Med. 40(12):1072-82

Greer MA, Goodman G, Pleus RC, Greer SE. 2002. Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. Environ Health Perspect. 110(9):927-37

Gross, E.A., Swenberg, J.A., Fields, S., and Popp, J.A. 1982. Comparative morphometry of the nasal cavity in rats and mice. J. Anat. 135, 83-88.

Hawley, J.K. 1985. Assessment of health risk from exposure to contaminated soil. Risk Analysis 5(4):289-302.

Harrington, N.W., Curry, C.L., and P.S. Price. 1995. The MicroExposure® Event Modeling Approach to Probabilistic Exposure Assessment. Paper No. 95-TA42.03. Proceedings of the 88th Annual Meeting of the Air and Waste Management Association. San Antonio, Texas, USA. June.

Hodgson, Ernest and P.E. Levi. 1987. Textbook of Modern Toxicology. Toxicology Program, Northern Carolina State University. New York: Elsevier Publishing.

Holmes, K.K., J.C. Kissel, and K.Y. Richter. 1996. (prepublication draft, cited in EPA, 1997)

ICH. (International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use). 1998. Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing). Recommended for Adoption at Step 4 of the ICH Process on 2 September 1998 by the ICH Steering Committee.

IRIS. 2003. Integrated Risk Information System. www.epa.gov/iris/

Keenan, R.E., P.S. Price, J. McCrodden, and E.S. Ebert. 1996. Using a microexposure event analyses to model potential exposures to PCBs through ingestion of fish from the Upper Hudson River. In: Organohalogen Compounds: Proceedings Dioxin '96-16th International Symposium on Chlorinated Dioxins and Related Compounds, Amsterdam, The Netherlands. *Organohalogen* 30:61-65.

Kelsh M, Buffler P, Daaboul J, Rutherford G, Lau Edmund, Exuzides A, Cahill J, Palmer L, Lorey F. 2002. Primary congenital hypothyroidism and newborn thyroid function among residents of a southern California community. Submitted to JOEM and as comments to Cal EPA OEHHA.

Kissel, J.C., K.Y. Richter, and R.A. Fenske. 1996. Field measurement of dermal soil lading attributable to various activities: Implications for exposure assessment. Risk Analysis 16(10):115-125.

Lamm SH, Braverman LE, Li FX, Richman K, Pino S, Howearth G. 1999. Thyroid health status of ammonium perchlorate workers: a cross-sectional occupational health study. J Occup Environ Med. 41(4):248-60

Lamm SH, Doemland M. 1999. Has perchlorate in drinking water increased the rate of congenital hypothyroidism? J Occup Environ Med. 41(5):409-11

Lang, L. 1995. Strange brew: assessing risk of chemical mixtures. Environmental Health Perspectives. 103(2). http://ehpnet1.niehs.nih.gov/docs/1995/103-2/focus.html.

Lawrence JE, Lamm SH, Pino S, Richman K, Braverman LE. 2000. The effect of short-term low-dose perchlorate on various aspects of thyroid function. Thyroid 10(8):659-63

Li FX, Squartsoff L, Lamm SH. 2001. Prevalence of thyroid diseases in Nevada counties with respect to perchlorate in drinking water. J Occup Environ Med. 43(7):630-4

Li Z, Li FX, Byrd D, Deyhle GM, Sesser DE, Skeels MR, Lamm SH. 2000. Neonatal thyroxine level and perchlorate in drinking water. J Occup Environ Med. 42(2):200-5

Mayes, Brian A., George L. Brown, Frank J. Mondello, Kevin W. Holtzclaw, Stephen B. Hamilton, and Arthur A. Ramsey. 2002. Dermal Absorption in Rhesus Monkeys of Polychlorinated Biphenyls from Soil Contaminated with Aroclor 1260. Reg. Tox. & Pharm. 35: 289-295.

Nessel C.S., Lewis S.C., Stauber K.K. and Adgate J.L. 1995. Subchronic to Chronic Exposure Extrapolation: Toxicologic Evidence for a Reduced Uncertainty Factor Hum. Ecol. Risk Assess. Vol. 1, No. 5, pp. 516-526.

Nosek, J.A., S.R. Craven, J.R. Sullivan, S.S. Hurley, and R.E. Peterson. 1992. Toxicity and reproductive effects on 2,3,7,8-tetrachlorodibenzo-p-dioxin in ring-necked pheasant hens. Journal of Toxicology and Environmental Health. 35: 187-198.

NRC. National Research Council. 1983. Risk Assessment in the Federal Government: Managing the Process. National Academy Press.

NTP. 1984. Toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (inhalation studies). National Toxicology Program. NTP TR 288.

NTP. National Toxicology Program. 1989. Toxicity Study of Acetone, "Summary of Information on Acetone" (NTPTS2).

OSHA. 1995. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000, Table Z-l.

Park, RM. 2001. Perchlorate health effects in the epidemiological literature [with cover letter]. Cincinnati OH: National Institute for Occupational Safety and Health, Education and Information Division – Risk Evaluation Branch.

Piikivi, L. and U. Tolonen. 1989a. EEG findings in chlor-alkali workers subjected to low long term exposure to mercury vapor. Br. J. Ind. Med. 46: 370-375.

Piikivi, L. and H. Hanninen. 1989b. Subjective symptoms and psychological performance of chlorine-alkali workers. Scand. J. Work Environ. Health. 15: 69-74.

Piikivi, L. 1989c. Cardiovascular reflexes and low long-term exposure to mercury vapor. Int. Arch. Occup. Environ. Health. 61: 391-395.

Price, P.S., C.L. Curry, P.E. Goodrum, M.N. Gray, J.I. McCrodden, N.W. Harrington, H. Carlson-Lynch, and R.E. Keenan. 1996. Monte Carlo modeling of time-dependent exposures using a Microexposure Event approach. Risk Anal. 16(3):339-348.

Price, P.S., R.E. Keenan, and B. Schwab. 1999. Defining the interindividual (intraspecies) uncertainty factor. *Hum. Eco. Risk Assess*. 5(5):1023-1033.

Renwick, A.G. and N.R. Lazarus. 1998. Human variability and noncancer risk assessment – an analysis of the default uncertainty factor. Regul. Toxicol. Pharmacol. 27:3-20.

Restum, J.C., S.J. Bursian, J.P. Giesy, J.A. Render, W.G. Helferich, E.B. Ship and D.A. Verbrugge. 1998. Multigenerational Study of the Effects of Consumption of PCB-Contaminated Carp from Saginaw Bay, Lake Huron, on Mink. 1. Effects on Mink

Reproduction, Kit Growth and Survival, and Selected Biological Parameters. Journal of Toxicology and Environmental Health Part A 54:343-375.

Roy, T.A., J.J. Yang, A.J. Krueger, and C.R. Mackerer. 1990. Percutaneous absorption of neat 2,3,7,8-tetrachlorogdibenzo-p-dioxin (TCDD) and TCDD sorbed on soils. Toxicology 10(1):308.

SAB. 1997. An SAB Report: Guidelines for Cancer Risk Assessment. Sept. SAB-EHC-97-010.

SAB. 1998. An SAB report: Review of the health risk assessment of 1,3-butadiene. U.S. Environmental Protection Agency, Science Advisory Board, Environmental Health Committee. EPA-SAB-EHC-99-003. November.

Sample, B.E., D.M. Opresko, and G.W. Suter II. 1996. Toxicological Benchmarks for Wildlife: 1996 Revision. Risk Assessment Program, Health Sciences Research Division, Oak Ridge National Laboratory. ES/ER/TM-86/R3.

SCF. Scientific Committee on Food. 2002. Opinion of the Scientific Committee on Food on Fusarium toxins. Part 6: Group evaluation of T-2 toxin, HT-2 toxin, nivalenol and deoxynivalenol. European Commission Health and Consumer Protection Directorate-General. SCF/CS/CNTM/MYC/27 Final. February.

Schwartz J, Jewell NP. 2001. Gestational exposure to perchlorate is associated with measures of decreased thyroid function in a population of California neonates. Masters thesis submitted to UC Berkeley School of Public Health.

Sheppard, S.C. 1995. Parameter values to model the soil ingestion pathway. Environ. Monit. Assess. 34:27-44.

Simon, T.W. 1999. Two-dimensional Monte Carlo simulation and beyond: A comparison of several probabilistic risk assessment methods applied to a Superfund site. Hum. Ecol. Risk Assess. 5 (4): 823-843.

Stanbury JB, Wyngaarden JB. 1952. Effect of perchlorate on the human thyroid gland. Endocrinology 533-539.

Stehr-Green., P.A., E. Welty, and V.W. Burse. 1988. Human exposure to polychlorinated biphenyls at toxic waste sites: investigations in the United States.
Arch Environ Health. Nov-Dec;43(6):420-4.

Stanek, E.J., Calabrese, E.J., Barnes, R. and Pekow, P. 1997. Soil ingestion in adults--results of a second pilot study. Ecotoxicol Environ Saf. 36(3):249-57.

Stevens, K.R. L. and Mylecraine. 1994. Issues in chronic toxicology. In Principles and Methods of Toxicology, Third Edition. A. Wallace Hayes, editor. Raven Press, New York. Pages 673-695.

Suter, II, G.W. and C.L. Tsao. 1996. Toxicological Benchmarks for Screening Potential Contaminants of Concern for Effects on Aquatic Biota: 1996 Revision. Lockheed Martin Energy Systems. ES/ER/TM-96R2

Tucker, A.N., V.M. Sanders, D.W. Barnes, et al. 1982. Toxicology of trichloroethylene in the mouse. Toxicology. And Applied. Pharmacology. 62:351-357.

Uraih, L.C. and R.R. Maronpot. 1990. Normal histology of the nasal cavity and application of special techniques. Environmental Health Perspectives; Chemcials and Lung Toxicity, Upper Respiratory System. 85:187-209.

USACHPPM. U.S. Army Center for Health Promotion and Preventative Medicine. 2000. Standard Practice for Wildlife Toxicity Reference Values. Technical Guide No. 254. October.

Viscusi, W.K. and James T. Hamilton. April 1999. Are Risk Regulators Rational? Evidence from Hazardous Waste Cleanup Decisions (Working Paper 99-2). (Research support was provided under Cooperative agreement No. CR-823604-01 from the U.S. EPA Office of Policy, Planning, and Evaluation).

West, P.C., J.M. Fly, R.Marans, & F.Larhin. 1989a. Michigan Sport Anglers Fish Consumption Survey. Technical Report #1. (Natural Resources Sociology Research Lab)

West, P., J.M. Fly, R. Marans, and F. Larkin. 1989b. Michigan Sport Anglers Fish Consumption Survey. Supplement I – Non-Response Bias and Consumption Suppression Effect Adjustments. A Report to the Michigan Toxic Substance Control Commission. Natural Resource Sociology Research Lab Technical Report #2. September.

West, P.C., J.M. Fly, R.Marans, F.Larhin & D.Rosenblatt. 1993. 1991-1992 Michigan Sport Anglers Fish Consumption Study. Technical Report #6. (University of Michigan School of Natural Resources)

Wester, R.C., H.I.Maibach, L.Sedik & J.Melendres. 1993. Percutaneous absorption of PCBs from soil: In vivo rhesus monkey, in vitro skin, and binding to powdered human stratum corneum. J.Tox.& Env. Health 39:375-82.

WHO (1998). Environmental Health Criteria: Acetone. World Health Organization, International Programme On Chemical Safety. EHC 207. Geneva, Switzerland.

Wolf, O. 1976. Cancer Morbidity Amongst Chemical Workers From A Former Naphthalene Cleaning Plant [Translated From The German By The Uk Hse]. German Title: Kreberkrankungen Bei Chemiearbeitern Einer Ehemaligen Naphthalinreinigung. Dt. Gesundh.-Wesen.31:996-999. Hse Translation Number 15358 (A).

Wolf, O. 1978. Carcinoma Of The Larynx In Workers Engaged In The Purification Of Naphthalene [Translated From The German By The Uk Hse]. Zeitschrift Fur Die Gesamte Hygiene Und Ihre Grenzgebiete 24 (10: 737-739. Hse Translation Number 15329 (A).

Wu, C. and J. Schaum. 2000. Exposure assessment of trichloroethylene. Environmental Health Perspectives, Supplement 2 108:359-363.

Wyngaarden JB, Wright BM, Ways P. The effect of certain anions on the accumulation and retention of iodide by the thyroid gland. Endocrinology (1952) 50:537-549
Wyngaarden JB, Stanbury JB, Rapp B. The effects of iodide, perchlorate, thiocyanate and nitrate administration upon the iodide concentrating mechanism of the rat thyroid. Endocrinology (1953) 52:568-574

Xiao Li F, Byrd DM, Deyhle GM, Sesser DE, Skeels MR, Katkowsky SR, Lamm SH. Neonatal thyroid-stimulating hormone level and perchlorate in drinking water. Teratology 2000 Dec;62(6):429-31